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HIGH PRODUCTION VOLUME (HPV)

CHEMICAL CHALLENGE PROGRAM

TEST PLAN

FOR

ALIPHATIC ESTERS CATEGORY

Prepared by:

American Chemistry Council's
Aliphatic Esters Panel

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EXECUTIVE SUMMARY

The American Chemistry Council's (ACC) Aliphatic Esters Panel (Panel) and its member companies, hereby submit for review and public comment the test plan for the "aliphatic esters" category of chemicals, under the Environmental Protection Agency's (EPA's) High Production Volume (HPV) Chemical Challenge Program. It is the intent of the Panel and its member companies to use existing available public and company data in conjunction with scientific judgement/analysis to adequately characterize the Screening Information Data Set (SIDS) of human health, environmental fate and effects, and physicochemical property endpoints for this category.

This test plan addresses the 45 HPV aliphatic esters listed in Table 1. Aliphatic esters generally are produced from reaction of carboxylic acids (monoacids and diacids) and various alcohols (i.e., monoalcohols, dihydroxy- and trihydroxy alcohols, and polyols). The aliphatic esters have been divided into five group subcategories (i.e., monoesters, diesters, glycol esters, sorbitan esters and polyol esters) according to structural commonalities of the alcohol and acid portions of the esters. The organization of the HPV substances into five groups is appropriate because it helps differentiate the aliphatic esters in regards to their physicochemical properties, chemical characteristics and biological/toxicological activity based on structural similarities. It also represents a rational structural approach to systematically compare existing data, to justify "read-across" assessments for structurally related esters, and to develop a stepwise strategy test plan for the HPV aliphatic esters according to ester group types.

The five proposed groups and their testing rationales are described below.

<u>Group A - Aliphatic esters, comprised of monoacids and monoalcohols - "Monoesters"</u>

Three HPV aliphatic esters were organized into Group A. The feature that distinguishes this group is that they are simple "monoesters" comprised of monocarboxylic acids (typically natural fatty acids) and simple monoalcohols. These esters are reaction products of palmitic, stearic or tall oil fatty acids, and C8 or C13 alcohols. These esters are used as lubricants, emollients, cosmetic ingredients or solvents. In addition, the three HPV esters are very structurally similar to a number of alkyl fatty acid esters that are commonly used in the cosmetic industry [e.g., butyl stearate, octyl stearate, decyl oleate, myristyl stearate, and isocetyl stearate] and for which extensive toxicity data exist. For this reason, these five alkyl fatty acid esters as well as another 2-ethylhexyl fatty acid ester were included as reference compounds to provide useful data for read-across assessments.

Physicochemical properties and environmental fate for all group members were calculated using appropriate QSAR models and supplemented with measured data from the literature or from company data. No additional physicochemical properties and environmental fate testing are proposed for this group.

Supplemented with published data for six structurally related reference alkyl fatty acid esters, there was sufficient toxicity information available to make hazard assessments for the human health effects and environmental toxicity (SIDS endpoints) for the HPV substances in this group. Given the similar chemical/structural features and similar carbon-number range between the three HPV monoesters and the six reference alkyl fatty acid esters, it was justifiable to utilize the available data to "read-across" and to bridge the toxicity data gaps for the HPV esters in Group A. No additional mammalian and environmental toxicity testing are proposed for this group.

Group B - Aliphatic esters, comprised of diacids and monoalcohols - "Diesters"

Thirteen HPV aliphatic esters fell into Group B. The distinguishing feature of this group is that they are diester derivatives of the common diacids: namely, maleic (C4), adipic (C6), azelaic (C9) and sebacic (C10) acids. The alcohol portion in most of the diesters falls in the C7-C13 carbon number range. In addition, a majority of the HPV diesters in this group fall within the carbon range of C22-C32 and have similar properties and structural characteristics. The diesters in this group have widespread use as lubricants, plasticizers, and solvents.

In addition to the available data for various HPV diesters in this group, there was published information for other structurally related diesters which provided useful supplementary data to help bridge the toxicity data gaps for the other HPV diesters. The non-HPV reference compounds included: maleic acid, dibutyl ester; adipic acid, di-C7-9 branched and linear alkyl ester; adipic acid, bis(2-ethylhexyl) ester; and adipic acid, dibutyl ester.

Measured physicochemical property data were available for many of the diesters. In addition, computer estimation models were used to calculate physicochemical property and environmental fate data for the Group B substances. The calculated data were obtained using the EPIWIN and EQC models that the EPA has cited for use in the HPV Chemical Challenge Program. The experimental and calculated values were sufficient to provide the necessary information on the physicochemical and fate properties of the HPV esters in Group B. No additional testing for physicochemical and fate properties is proposed for this group.

The available datasets of mammalian toxicity information (e.g., acute, repeated dose, genetic toxicity, reproductive/developmental toxicity) from both the HPV diesters and the non-HPV reference compounds were sufficient to cover the SIDS data endpoints for the range of diesters in this group and to permit "read-across" assessment for untested HPV members. Especially useful were the extensive toxicity data available for maleic acid, dibutyl ester; adipic acid, bis(2-ethylhexyl) ester; adipic acid, tridecyl ester; and adipic acid, di-C7-9 branched and linear alkyl esters; sebacic acid, bis(2-ethylhexyl) ester. These diesters covered the carbon number range for the HPV diesters in this group and provided useful toxicity data to make "read-across" assessments and to bridge data gaps. No additional mammalian toxicity testing is proposed for this group.

Similarly, sufficient aquatic toxicity and biodegradation data were available from both the HPV diesters and the non-HPV reference diesters to cover the carbon-number range within this group and to allow for "read-across" assessments of aquatic toxicity and biodegradation for the other HPV members. No additional environmental toxicity and biodegradation testing are proposed for this group.

Group C - Aliphatic esters, comprised of monoacids and dihydroxy alcohols - "Glycol Esters"

Eight HPV aliphatic esters were organized into Group C. The differentiating feature of this group is that they are ester derivatives of ethylene glycol and propylene glycol (the alcohol portion of the ester molecule). Fatty acids (C6-C18) make up the carboxylic acid portion of the ester molecule, with oleic and stearic acids being the most common. The HPV glycol esters covered the C20-C40 carbon number range. The commonalities of the ethylene glycol or propylene glycol substructure and the natural fatty acids (e.g., oleic and stearic acids) justify grouping the HPV glycol esters together on toxicological grounds. The glycol esters have widespread use in lubricant, cosmetic and solvent applications.

The published data on five structurally related non-HPV glycol esters were also reviewed and were used as supplementary information to help bridge the toxicity of substances in this group. These non-HPV reference glycol esters included: heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol; triethylene glycol, diheptanoate; propylene glycol, monostearate; propylene glycol, dilaurate; and propylene glycol, diisostearate. It should be noted that the propylene glycol stearates, oleates and laurates, which are commonly used in many cosmetics, were very structurally similar to many of the HPV substances in Group C. It is noteworthy that propylene glycol stearate has been approved for a variety of pharmaceutical applications and is "Generally Recognized as Safe" (GRAS) for food use. Thus, the reference glycol ester compounds provided useful toxicity information for "read-across" assessments.

Physicochemical properties and environmental fate for all group members were calculated using appropriate QSAR models and supplemented with measured data from the literature or from company data. No additional physicochemical and fate properties studies are proposed for this group.

The available mammalian toxicity information from both the HPV glycol esters and the non-HPV reference compounds were sufficient to cover the SIDS data endpoints for the HPV substances in this group and to permit "read-across" assessments for the untested members. Taken into consideration also were the published health safety assessments for thirteen propylene glycol fatty acid esters (Johnson, 1999). To complete the reproductive/developmental health hazard assessment of this group, a technical discussion document is proposed. No additional mammalian toxicity testing is proposed for this group.

There were sufficient ecotoxicity data available to indicate that the glycol esters have a low order of acute toxicity to aquatic organisms. Available information from various studies also indicate that glycol esters in this group undergo extensive biodegradation. In addition, there were published data to indicate that the constituent free ethylene or propylene glycol and free fatty acids, generated from ester cleavage of the parent glycol esters, are likely to be extensively biodegraded. No additional environmental toxicity and biodegradability testing are proposed for substances in this group.

Group D - Aliphatic esters, comprised of monoacids and sorbitan - "Sorbitan Esters"

Six HPV aliphatic esters were organized into Group D. These substances have the distinguishing feature that sorbitan comprises the alcohol portion of the ester. Sorbitan is derived from the carbohydrate sugar, sorbitol, and has four hydroxy groups available for esterification. The acid portion of the HPV sorbitan esters is comprised mainly of natural fatty acids (e.g., lauric, stearic and oleic acids). Four of the HPV substances are sorbitan monoesters and two have multiple ester linkages (i.e., sorbitan sesquioleate and sorbitan trioleate). Three of the HPV substances (i.e., the oleate esters of sorbitan) were essentially the same except for the degree of esterification.

Sorbitan esters are non-ionic surfactant-active agents that typically find use as emulsifiers, stabilizers and thickeners in foods, cosmetics, medical products, lubricants and other applications. Many of the HPV sorbitan esters have widespread use in cosmetic and pharmaceutical applications. More importantly, a substantial amount of toxicity data and health safety information have been published for the sorbitan esters. The available mammalian toxicity data on the HPV and non-HPV sorbitan esters from the literature and from proprietary sources were sufficient to cover the SIDS data endpoints for the HPV substances in this group and to permit "read-across" assessments for the untested HPV members. Also taken into consideration were the comprehensive health safety assessment reviews reported for the sorbitan esters (Elder, 1985a; CIR, 1999). Results with sorbitan monostearate in chronic two-year feeding studies indicated that this material caused no adverse effects on gestation and fertility. Results from two reproductive/developmental studies indicated that sorbitol did not cause reproductive or developmental toxicity. To complete the reproductive and developmental health hazard assessment for the sorbitan esters of this group, a technical discussion document is proposed. No additional mammalian toxicity testing is proposed for this group.

Physicochemical properties and environmental fate for all members were calculated using appropriate QSAR models and supplemented with measured data. No additional physicochemical and fate studies are proposed for this group.

There were sufficient ecotoxicity and biodegradation data to indicate that the sorbitan esters in this group are not acutely toxic to aquatic organisms and that they are extensively biodegraded in the aerobic aqueous environment. No additional environmental toxicity and biodegradability testing are proposed for substances in this group.

Group E - Aliphatic esters, comprised of monoacids and trihydroxy or polyhydroxy alcohols (polyols) - "Polyol Esters"

Fifteen HPV aliphatic esters were classified in Group E. The substances in this group represented structurally related "polyol esters" in which the fatty acids were linked to one or more of the multiple hydroxyl groups present in the polyol (alcohol portion of ester). The polyol consisted of either pentaerythritol (PE), trimethylolpropane (TMP) or dipentaerythritol (diPE). The fatty acids ranged from C5-C18 in carbon number and often were comprised of natural fatty acids such as oleic and stearic acids. The polyol esters are used as synthetic lubricants, hydraulic fluids, and cosmetic ingredients, and often find use in high temperature applications (e.g., transformer coolants, oven chain oils, high temperature greases).

Physicochemical properties and environmental fate for all group members were calculated using appropriate QSAR models and supplemented with measured data. The experimental and calculated values were sufficient to provide the necessary information on the physicochemical and fate properties of the HPV esters in this group. No additional testing for physicochemical and fate properties is proposed.

In addition to the available data for various HPV polyol esters, there were substantial proprietary data for seven structurally related polyol esters which provided useful supplementary data to help bridge the toxicity gaps for the other HPV polyol esters. The non-HPV reference compounds included three TMP esters, three PE esters and one diPE ester. The available mammalian toxicity information (e.g., acute, repeated dose, genetic toxicity, reproductive/developmental toxicity) from both the HPV polyol esters and non-HPV reference compounds were sufficient to cover the SIDS data endpoints for the range of polyol esters in this group and to permit "read-across" assessments for the other HPV members. The HPV ester, decanoic acid, ester with 2-ethyl-2-(hydroxymethyl)-1,2-propanediol, has been evaluated for reproductive/developmental toxicity. According to the sponsor of the study, the test material showed no reproductive/developmental effects. To complete the reproductive/developmental health hazard assessment of this group, a technical discussion document is proposed. No additional mammalian toxicity testing is proposed for this group.

Sufficient aquatic toxicity and biodegradation data were available from both the HPV polyol esters and the non-HPV reference polyol esters to cover the range of ester types (e.g., TMP, PE) within this group and to allow for "read-across" assessments of aquatic toxicity and biodegradation for the other HPV members. The polyol esters were not acutely toxic to aquatic organisms and they were extensively biodegraded in the aqueous environment. No additional environmental toxicity and biodegradability studies are proposed for this group.

LIST OF MEMBER COMPANIES ON THE ALIPHATIC ESTERS PANEL

The American Chemistry Council's Aliphatic Esters Panel includes the following member companies:

Aristech Chemical Corporation
Arizona Chemical Company
BASF Corporation
BF Goodrich Company
Cognis Corporation
Crompton Corporation
Cytec Industries Inc.
E.I. duPont de Nemours & Company, Inc.
ExxonMobil Chemical Company
Goldschmidt Chemical Corporation
Hercules Inc.
Inolex Chemical Company
Kaufman Holdings Corporation (formerly Hatco)
Quaker Chemical Company
Rohm and Haas Company
Stepan Company
The CP Hall Company
Uniquema
Velsicol Chemical Corporation

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TEST PLAN FOR THE ALIPHATIC ESTERS CATEGORY

1.0 INTRODUCTION

The American Chemistry Council's (ACC) Aliphatic Esters Panel (Panel) and its member companies have committed voluntarily to develop a Screening Information Data Set (SIDS) (i.e., physicochemical data, environmental fate and effects, and mammalian health effects) for the "aliphatic esters" category of chemicals, listed under the Environmental Protection Agency's (EPA's) High Production Volume (HPV) Chemical Challenge Program.

This test plan sets forth how the Aliphatic Esters Panel intends to address the testing information for the 45 aliphatic ester substances listed in Table 1. The chemical structures of the aliphatic esters are given in Figure 1. The test plan identifies the individual aliphatic esters based on CAS numbers and their acid and alcohol functional structures, identifies structurally related esters that fall systematically under five group subcategories, identifies existing data of adequate quality for substances included in the group subcategories and provides our rationale for applying the available SIDS data to characterize the hazards of the category members. The objective of this effort is to identify and to adequately characterize the physicochemical properties, human health and environmental fate and effects for the aliphatic esters in compliance with the EPA HPV Chemical Challenge Program.

The document also provides the basis for the determination of chemical category and the justification for dividing the aliphatic esters in five group subcategories, based on the structurally similar carboxylic acid and alcohol functionalities.

The data from this HPV category will be used to inform the public about the potential health effects of the aliphatic esters. Developing a data matrix with reliable studies and applying justifiable read-across assessments will help provide a sufficiently robust data set to characterize the endpoints in the HPV Chemical Challenge Program without significant need for further testing. This approach to the resourceful use of existing data will help minimize the use of animals for testing and at the same time adequately assess the potential hazards in the aliphatic esters category.

2.0 DESCRIPTION FOR THE ALIPHATIC ESTERS CATEGORY

2.1 Aliphatic Esters Category Analysis

This test plan addresses 45 substances which fall under the "aliphatic esters" category within the HPV Challenge Program. These aliphatic esters have been systematically organized in five groups (Group A, B, C, D, E), based on chemical structural similarities of the carboxylic acid and alcohol groups. The Panel and its member companies believe that organization of the aliphatic esters into the five group subcategories is important and represents a rational structural approach to evaluating the existing data and to developing a stepwise strategy test plan based on consideration of chemistry and structural commonalities among each group of esters. The aliphatic ester members are presented in Table 1 by their groups, TSCA HPV designated names and CAS registry numbers. The chemical structures are depicted in Figure 1.

<u>Table 1</u> Aliphatic Esters Category Substances *(divided into five Groups)*

Group A: Aliphatic esters, comprised of monoacids and monoalcohols - "Monoesters"

Chemical Name	CAS Number
Palmitic acid, 2-ethylhexyl ester	29806-73-3
Stearic acid, tridecyl ester	31556-45-3
Fatty acids, tall oil, 2-ethylhexyl esters	68334-13-4

Group B: Aliphatic esters, comprised of diacids and monoalcohols - "Diesters"

Chemical Name	CAS Number
Azelaic acid, bis(2-ethylhexyl)ester	103-24-2
Maleic acid, bis(1,3-dimethylbutyl)ester	105-52-2
Sebacic acid, dimethyl ester	106-79-6
Adipic acid, bis(1-methylheptyl)ester	108-63-4
Sebacic acid, bis(2-ethylhexyl)ester	122-62-3
Adipic acid, bis[2-(2-butoxyethoxy)ethyl]ester	141-17-3
Maleic acid, bis(2-ethylhexyl)ester	142-16-5
Adipic acid, diisooctyl ester	1330-86-5
Adipic acid, diisopropyl ester	6938-94-9
Adipic acid, ditridecyl ester	16958-92-2
Adipic acid, diisodecyl ester	27178-16-1
Azelaic acid, diisodecyl ester	28472-97-1
Adipic acid, diisononyl ester	33703-08-1

Group C: Aliphatic esters, comprised of monoacids and dihydroxy alcohols -"Glycol esters"

Chemical Name	CAS Number
Oleic acid, propylene ester	105-62-4
Stearic acid, 2-hydroxyethyl ester	111-60-4
Stearic acid, ethylene ester	627-83-8
Hexanoic acid, 2-ethyl-, diester with tetraethylene glycol	18268-70-7
9-Octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediyl ester	42222-50-4
9-Octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol	67989-24-6
Decanoic acid, mixed diesters with octanoic acid and triethylene glycol	68583-52-8
Heptanoic acid, oxybis(2,1-ethanediyloxy-2,1-ethanediyl) ester	70729-68-9

Group D: Aliphatic esters, comprised of monoacids and sorbitan -"Sorbitan esters"

Chemical Name	CAS Number
Sorbitan, monolaurate	1338-39-2
Sorbitan, monostearate	1338-41-6
Sorbitan, monooleate	1338-43-8
Sorbitan, sesquioleate	8007-43-0
Sorbitan, trioleate	26266-58-0
Fatty acids, coco, monoesters with sorbitan	68154-36-9

Table 1 **Aliphatic Esters Category Substances** ***(divided into five Groups)*** **(Continued)**

Group E: Aliphatic esters, comprised of monoacids and trihydroxy or polyhydroxy alcohols (polyols) – "Polyol Esters"

Chemical Name	CAS Number
Nonanoic acid, triester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol	126-57-8
Decanoic acid, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol octanoate	11138-60-6
9-Octadecenoic acid (Z)-, 2-ethyl-2-[[(1-oxo-9-octadecenyl)oxy]methyl]-1,3-propanediyl ester, (Z)-	57675-44-2
9-Octadecenoic acid (Z)-, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol	70024-57-6
Pentaerythritrol, tetrastearate	115-83-3
Nonanoic acid, neopentanetetrayl ester	14450-05-6
Carboxylic acids, C5-9, hexaesters with dipentaerythritol	67762-52-1
Carboxylic acids, C5-9, tetraesters with pentaerythritol	67762-53-2
Fatty acids, C14-18 and C16-18 unsatd, triesters with trimethylolpropane	68002-79-9
Decanoic acid, mixed esters with heptanoic acid, isovaleric acid, octanoic acid and pentaerythritol	68130-51-8
Decanoic acid, mixed esters with heptanoic acid, octanoic acid and trimethylolpropane	68130-53-0
Fatty acids, tall oil, tetra esters with pentaerythritol	68334-18-9
Fatty acids, C5-10, esters with pentaerythritol	68424-31-7
Fatty acids, C5-10, mixed esters with pentaerythritol and valeric acid	68424-34-0
Linseed oil, ester with pentaerythritol	68648-28-2
Fatty acids, C5-10, esters with dipentaerythritol	70983-72-1

2.2 Rationalization for Organizing the Aliphatic Esters Category into Five Groups

Aliphatic esters are generally defined as reaction products of carboxylic acids and alcohols. They can be synthesized by a variety of methods. They are commercially produced for a broad range of applications (e.g., as lubricants, solvents, plasticizers, emulsifiers, cosmetic ingredients). In examining the forty five aliphatic esters on the HPV list, there were sufficient structural similarities and/or differences among the substances to warrant systematically organizing them into five group subcategories.

The justification for dividing the esters into the five groups was based on similarities in their chemical structures, which depended mainly on whether the carboxylic acid portion of the ester was derived from monocarboxylic acids, fatty acids or dicarboxylic acids (e.g., adipic, sebacic, azeleic, maleic acid) and on whether the alcohol portion was derived from monohydroxy alcohols (monoalcohols, mainly aliphatic), dihydroxy alcohols (e.g., glycols, diols), trihydroxyl or polyhydroxy alcohols (e.g., trimethylolpropane, pentaerythritol, dipentaerythritol or sorbitan). The monoacids and diacids are aliphatic or alkenyl in nature and most of the monocarboxylic acids include common natural fatty acids such as palmitic, stearic, oleic, and linoleic acids.

In addition, the organization of the HPV aliphatic esters into five group subcategories is quite appropriate because it also helps to differentiate the esters in regards to their physicochemical properties, chemical characteristics and biological activity based on structure. For example, monoesters comprised of a simple monocarboxylic acid and a simple alcohol have a single ester linkage. For a homologous series, monoesters having alcohol portions of low carbon number (e.g., methyl, ethyl, propyl) generally are expected to have low viscosity characteristics, greater water solubility and greater volatility than monoesters having longer carbon-length (e.g., C10-C18) alcohol groups. However, as the carbon numbers in the carboxylic acid or alcohol increase, the corresponding esters are likely to have lower water solubility, greater lipophilicity, less volatility, higher boiling points, and greater thermal stability. For many aliphatic esters, their poor water solubility may be an important factor to consider in assessing aquatic toxicity.

The greater degree of esterification in polyol esters helps to explain why they have lower volatility, higher thermal stability and lower water solubility than the corresponding simple monoesters. The multiple ester linkages in the diesters, glycol esters and sorbitan esters also account for similar physicochemical properties advantages that they have over monoesters. Hence, the organization and differentiation of the esters based on group type, acid and alcohol similarities, carbon length of acid/alcohol, degree of esterification, total carbon atoms, molecular weight, homologs, etc. provide a rational structural approach to assess the existing physicochemical property and environmental fate datasets and to justify "read-across" for similar ester group types.

The differentiation of the aliphatic esters based on group subcategories is very useful in assessing the potential difference in metabolism or hydrolysis, processes which lead to the generation of relatively non-toxic metabolites or degradation products. For example, the metabolism of sorbitan monooleate yields oleic acid (natural fatty acid), and sorbitan (a carbohydrate), both of which are safe to the environment and to humans. The occurrence of natural fatty acids in many of the aliphatic esters on the HPV list should be noted, especially since these fatty acids are expected to be generated from metabolism of the parent ester in the environment or in the body. Therefore, how readily aliphatic esters are metabolized to their fatty acid and alcohol components will be important to consider when assessing their environmental and human health effects and potential toxicity. Aliphatic esters with multiple ester linkages, such as the trimethylolpropane (TMP) or pentaerythritol (PE) esters, in some cases, may be slowly metabolized, as a result of possible steric hindrance.

Enzymatic hydrolysis potential is also a key determinant in evaluating biodegradability and aquatic toxicity since many of the natural fatty acids and many of the alcohols (such as sorbitan, ethylene glycol, normal alcohols) formed from cleavage of the ester are further metabolized to CO_2 or biomass and hence are considered safe.

The Panel and its member companies believe that organization of the aliphatic esters into the five group subcategories is important and represents a rational structural approach to evaulating the existing data and to developing a stepwise strategy test plan based on consideration of chemistry and structure commonality in the ester molecule.

The discussion that follows describes the basis for the group classification and describes in more detail the structural features and chemical characteristics which uniquely distinguish the five groups of aliphatic esters.

2.3 Group Classification of Aliphatic Esters Based on Acid and Alcohol Chemical Structures

Category Analysis and Group Subcategorization

<u>Group A - Aliphatic Esters, Comprised of Monoacids and Monoalcohols - "Monoesters"</u>

The Group A substances are comprised of a monocarboxylic acid or fatty acid, such as palmitic, stearic, oleic and linoleic acid and a monoalcohol, such as 2-ethylhexyl alcohol or tridecyl alcohol. They are often termed as "monoesters" and are synthesized from simple aliphatic acid (e.g., fatty acids) and simple monoalcohols. Three esters on the HPV list that fall into Group A are:

Group A "Monoesters" - Chemical Name *	CAS Number	Carbon Number in acid	Carbon Number in alcohol	Total carbons in Ester	MW
palmitic acid, 2-ethylhexyl ester	29806-73-3	C16	C8	C24	369
fatty acid, tall oil, 2-ethylhexyl ester (major fatty acids in tall oil are oleic and linoleic acids)	68334-13-4	C18	C8	C26	393-395
stearic acid, tridecyl ester	31556-45-3	C18	C13	C31	467

*The esters in the above table are presented in ascending order of the total carbon numbers in the ester product rather than in the order of their CAS number as in Table 1. It is hoped that presentation of the esters based on carbon number as well as structural similarities in acid and alcohol portions of the esters will be useful for structure activity relationships for the HPV assessment of the aliphatic esters.

Group A esters differ from the other four groups because they are simple monoesters derived from a monofunctional alcohol, such as 2-ethylhexyl alcohol (C8-alcohol) or tridecyl alcohol (C13 alcohol) and fatty acids such as palmitic, stearic, oleic or linoleic acid. Metabolism of the parent esters is expected to yield the corresponding fatty acids and alcohols. The fatty acids are naturally occurring and have a low order of toxicity (Cragg 2001a,b; Chow 1999; Johnson, 1999). The biological effects for 2-ethylhexyl alcohol (BIBRA, 1990; Bevan 2001b) and tridecyl alcohol (Bevan 2001b; HPV Challenge Program 2001) have been reviewed and both have been reported to have a low order of toxicity.

Group B - Aliphatic Esters, Comprised of Diacids and Monoalcohols – "Diesters"

The Group B substances are comprised of aliphatic esters derived from linear diacids and monofunctional alcohols. The diacids include maleic (C4), adipic (C6), azelaic (C9) and sebacic (C10) acid. The monofunctional alcohols most common in the diesters are in the C8 to C13 carbon range, although methyl, isopropyl and butyl occur in some diesters. Thirteen esters on the HPV list that fall into Group B are:

Group B "Diesters" - Chemical Name *	CAS Number	Carbon Number in diacid	Carbon Number in alcohol	Total carbons in diester	MW
Maleic acid, bis(1,3-dimethylbutyl)ester	105-52-2	C4	C6	C16	284
Maleic acid, bis(2-ethylhexyl)ester	142-16-5	C4	C8	C20	341
Adipic acid, diisopropyl ester	6938-94-9	C6	C3	C12	230
Adipic acid, diisooctyl ester	1330-86-5	C6	C8	C22	370
Adipic acid, bis(1-methylheptyl)ester	108-63-4	C6	C8	C22	370
Adipic acid, bis[2-(2-butoxyethoxy)ethyl]ester	141-17-3	C6	C8	C22	435
Adipic acid, diisononyl ester	33703-08-1	C6	C9	C24	399
Adipic acid, diisodecyl ester	27178-16-1	C6	C10	C26	427
Adipic acid, ditridecyl ester	16958-92-2	C6	C13	C32	511
Azelaic acid, bis(2-ethylhexyl)ester	103-24-2	C9	C8	C25	412
Azelaic acid, diisodecyl ester	28472-97-1	C9	C10	C29	469
Sebacic acid, dimethyl ester	106-79-6	C10	C1	C12	230
Sebacic acid, bis(2-ethylhexyl)ester	122-62-3	C10	C8	C26	469

*The esters in the above table are presented in ascending order of the total carbon numbers and by diester type (e.g., maleate, alipate, azelate, and sebacate) rather than in the order of their CAS number as in Table 1. It is hoped that presentation of the esters based on carbon number as well as structural similarities in acid and alcohol portions of a homologous series for the diesters will be useful for structure activity relationships for the HPV assessment of the aliphatic esters.

There are two maleic acid, seven adipic acid, two azelaic acid and two sebacic acid diesters on the HPV list. Due to the physicochemical properties of the diesters (e.g., viscosity, pour point), they have widespread applications as lubricants, solvents, and plasticizers. The linear diacid portion of the diester contributes to the good viscosity index while branching in the alcohol portion provides good pour point characteristics. Because diesters have good polarity characteristics, they are useful as solvents. Most of the diesters in Group B are higher alkyl (>C8) adipates, azelates and sebacates and these diesters generally have a low order of toxicity (David et al., 2001).

Metabolism of the diesters in animals is expected to lead to the generation of corresponding diacids: namely, maleic, adipic, azelaic and sebacic acid and the corresponding linear or branched alcohol (e.g., 2-ethylhexyl, 1-methylheptyl, isooctyl, isononyl, isodecyl, tridecyl alcohols). These diacids and alcohols can further be metabolized and conjugated to products that are excreted in the urine (Cragg 2001a,b; Bevan 2001b; Thurman 1992). The diacids and alcohols have a low order of toxicity (Cragg, 2001a,b; Bevan 2001 a,b; HPV, 2001).

Group C - Aliphatic Esters, Comprised of Monoacids and Dihydroxy alcohols - "Glycol Esters"

The Group C substances are comprised of a monocarboxylic acid (generally natural fatty acids, e.g., oleic, stearic, C6-C10 fatty acids) and a dihydroxy alcohol (glycol or diol such as ethylene glycol, polyethylene glycol, propylene glycol, 2,2-dimethyl-1,3-propanediol). These esters are often referred to as "glycol or diol esters" or as "alkylidene or alkanediyl esters". Eight esters on the HPV list that fall into Group C are:

Group C "Glycol Esters" - Chemical Name *	CAS Number	Carbon Number in Acid	Carbon Number in dihydroxy alcohol	Total carbons in Ester	MW
Stearic acid, 2-hydroxyethyl ester	111-60-4	C18	C2	C20	329
Heptanoic acid, oxybis(2,1-ethanediyloxy-2,1-ethanediyl) ester	70729-68-9	C7	C8	C22	419
9-Octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol	67989-24-6	C18	C5	C23	368
Decanoic acid, mixed diesters with octanoic acid and triethylene glycol	68583-52-8	C8, C10	C6	C24	431
Hexanoic acid, 2-ethyl-, diester with tetraethylene glycol	18268-70-7	C8	C8	C24	447
Stearic acid, ethylene ester	627-83-8	C18	C2	C38	595
Oleic acid, propylene ester	105-62-4	C18	C3	C39	605
9-Octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediyl ester	42222-50-4	C18	C5	C41	633

*The esters in the above table are presented in ascending order of the total carbon numbers in the ester product rather than in the order of their CAS number as in Table 1. It is hoped that presentation of the esters based on carbon number as well as structural similarities in acid and alcohol portions of the esters will be useful for structure activity relationships for the HPV assessment of the aliphatic esters.

The rationale for grouping the glycol or diol esters is that they represent the ethylene/propylene glycol diesters in which the hydroxyl groups in the glycol are functionalized as ester derivatives. Esterification of the glycol with fatty acids such as stearic and oleic acid provides glycol diesters in the 38 to 41 carbon number range (MW 595-633), which typically make them relatively non-volatile and high boiling liquids with limited water solubility and with sufficient polar characteristics to make them useful as lubricants and solvents. In the case of the tri- and tetraethylene glycol diesters, the ether linkage in the polyalkylene portion of the glycol also imparts additional polar character to these glycol esters (Reck, 1999).

Glycol esters are susceptible to hydrolysis, both chemically and enzymatically (e.g., esterases in blood and serum, lipases and esterases in the gastrointestinal tract), yielding the corresponding free glycol (e.g., ethylene glycol, propylene glycol, or 2,2-dimethyl-1,3-propanediol) and fatty acids. The toxicity of these glycols has been extensively reviewed, especially for ethylene glycol (Cavender 2001). Propylene glycol has a low order of toxicity and has been used in humans as a diluent or solvent for water-insoluble drugs (Hardman-Goodman&Gilman, 2001).

Group D - Aliphatic Esters, Comprised of Monoacids and Sorbitan - "Sorbitan Esters"

The Group D substances are esters of monoacids, mainly common fatty acids, and sorbitan (which is derived from sorbitol - a natural carbohydrate sweetener). The fatty acids include lauric, stearic, oleic acids and coco fatty acids (mainly lauric and myristic acids). The hydroxy group in the sorbitan represents the alcohol portion of the ester linkage. Six esters on the HPV list that fall into Group D are:

Group D " Sorbitan Esters" - Chemical Name *	CAS Number	Carbon Number in Acid	Carbon Number in Alcohol	Total carbons in Ester	MW
Sorbitan, monolaurate	1338-39-2	C12	C6	C18	346
Fatty acids, coco, monoesters with sorbitan (main fatty acids are lauric and myristic acids)	68154-36-9	C12 C14	C6 C6	C18 to C20	346- 374
Sorbitan, monostearate	1338-41-6	C18	C6	C24	431
Sorbitan, monooleate	1338-43-8	C18	C6	C24	430
Sorbitan, sesquioleate	8007-43-0	C18	C6	C33	569
Sorbitan, trioleate	26266-58-0	C18	C6	C60	958

*The esters in the above table are presented in ascending order of the total carbon numbers in the ester product rather than in the order of their CAS number as in Table 1. It is hoped that presentation of the esters based on carbon number as well as structural similarities in acid and alcohol portions of the esters will be useful for structure activity relationships for the HPV assessment of the aliphatic esters.

The Group D esters are carbohydrate-derived esters since the ester linkage is connected to the hydroxy group(s) of sorbitan. Of the six aliphatic esters in Group D, four have single ester linkages (i.e., sorbitan monoester). There can be multiple ester linkages, as in the case of sorbitan sesquioleate and sorbitan trioleate. Multiple ester linkages with long-chain fatty acids increase lipophilicity and also tend to diminish water solubility. The sorbitan esters are non-ionic surfactant-active agents that typically find use as emulsifiers, stabilizers, and thickeners in foods, cosmetics and medical products.

Sorbitan esters do not represent a toxicological concern since they are derived from naturally occurring materials and the parent esters are ultimately metabolized back to these same natural constituents: namely, sorbitan and common fatty acids, both of which have low orders of toxicity (Elder, 1985a; CIR, 1999).

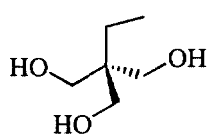
Group E - Aliphatic Esters, Comprised of Monoacid and Trihydroxy or Polyhydroxy Alcohols – "Polyol Esters"

The Group E substances are esters of monoacids, mainly common fatty acids, and trihydroxy or poly-hydroxy alcohols or polyols, such as pentaerythritol (PE), 2-ethyl-2-(hydroxymethyl)-1,3-propanediol or trimethylolpropane (TMP), and dipentaerythritol (diPE). The Group E substances often are referred to as "polyol esters." The polyol esters are unique in their chemical characteristics since they lack β-tertiary hydrogen atoms, thus leading to stability against oxidation and elimination. The fatty acids often range from C5-C10 to as high as C18 (e.g., oleic, stearic, isostearic, tall oil fatty acids) in carbon number and generally are derived from naturally occurring sources. Group E esters may have multiple ester linkages and may include mixed esters derived from different carbon-length fatty acid mixtures. Fifteen esters on the HPV list that fall into Group E are:

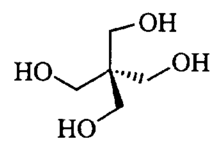
Group E "Polyol Esters" - Chemical Name *	CAS Number	Carbon Number in Acid	Total Carbons in Ester	MW
Decanoic acid, mixed esters with heptanoic acid, octanoic acid and trimethylolpropane (TMP Ester, C7, 8, 10 Acid)	68130-53-0	C7,8,10	31	513
Decanoic acid, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol octanoate (TMP Ester, C8, C10 Acid)	11138-60-6	C8,C10	24	415
Nonanoic acid, triester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (TMP TriEster, C9 Acid)	126-57-8	C9	33	555
Fatty acids, C14-18 and C16-18 unsatd, triesters with tri-methylolpropane (TMP TriEster, C14-18 satd, C16-18 unsatd Acid)	68002-79-9	C14-18	56	875
9-Octadecenoic acid (Z)-, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (TMP Monoester, Oleic C18 Acid)	70024-57-6	C18	24	417
9-Octadecenoic acid (Z)-, 2-ethyl-2-[[(1-oxo-9-octadecenyl)oxy]methyl]-1,3-propanediyl ester, (Z)- TMP Diester, Oleic C18 Acid)	57675-44-2	C18	60	928
Carboxylic acids, C5-9, tetraesters Pentaerythritol (PE TetraEster, C5-9 Acids)	67762-53-2	C5-9	33	523
Decanoic acid, mixed esters with heptanoic acid, isovaleric acid, octanoic acid and pentaerythritol (PE Mixed Ester, C7, 8 Acids)	68130-51-8	C7-C10	37	641
Fatty acids, C5-10, esters with pentaerythritol (PE Ester, C5-10 Acids)	68424-31-7	C5-10		613
Fatty acids, C5-10, mixed esters with pentaerhthritol and valeric acid	68424-34-0			
Nonanoic acid, neopentanetetrayl ester (PE TetraEster, C9 Acid)	14450-05-6	C9	41	697
Pentaerythritrol, tetrastearate (PE Tetraester, C18 Acid)	115-83-3	C18	77	1202
Linseed oil, ester with pentaerythritol (PE Ester, oleic, linoleic, linolenic acids)	68648-28-2	C18	77	1188
Fatty acids, tall oil, tetra esters with pentaerythritol (PE TetraEster, C18 oleic and linoleic acids)	68334-18-9	C18	77	1190
Fatty acids, C5-10, esters with dipentaerythritol (DiPE Ester, C5-10 Acids)	70983-72-1	C5-10	60	927
Carboxylic acids, C5-9, hexaesters with dipentaerythritol (diPE Esters, C5-C9 Acids)	67762-52-1	C5-9	60	955

*The esters in the above table are presented according to type of polyol ester (e.g., TMP, PE or diPE ester) and carbon number range of fatty acids in the ester rather than in the order of their CAS number as in Table 1. It is hoped that presentation of the esters based type of polyol ester and on fatty acid carbon numbers as well as structural similarities in acid and alcohol portions of the esters will be useful for structure activity relationships for the HPV assessment of the aliphatic esters.

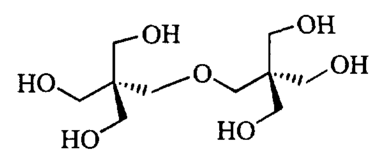
The lack of β-tertiary hydrogen atoms in the structure of the polyol esters makes them characteristically and chemically stable against oxidation and elimination in comparison to other ester classes or groups. For these reasons, trimethylolpropane (TMP) and pentaerythritol (PE) esters with fatty acids of C5 to C10 carbon-chain length have applications as synthetic lubricants for passenger car motor oil and military and civilian jet engines. TMP and PE esters of C18 acids (e.g., isostearic and oleic acids) also have found use in synthetic lubricant applications, including refrigeration lubricants and hydraulic fluids. Because of their higher thermal stability characteristics, they also find use in a variety of high temperature applications such as industrial oven chain oils, high temperature greases, fire resistant transformer coolants and turbine engines (Randles, 1999; Eisenhard, 1999).



Trimethylolpropane (TMP) or
2-ethyl-2(hydroxymethyl)-1,3-propanediol.



Pentaerythritol (PE)



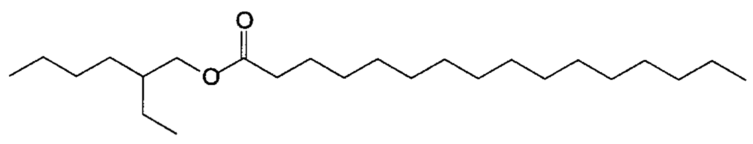
Dipentaerythritol (diPE)

Polyol esters that are extensively esterified also have greater polarity, less volatility and enhanced lubricity characteristics. Depending on the degree of esterification, the polyol esters can be resistant or slow towards chemical or enzymatic hydrolysis (i.e., esterase or lipases) as a result of steric hindrance. PE and diPE esters that are capable of being enzymatically hydrolyzed will generate pentaerythritol or dipentaerythritol, and the corresponding fatty acids which, for most of the Group E esters, are comprised mainly of oleic, linoleic and stearic acids as well as the fatty acids in the C5-10 carbon-length. Similarly, TMP esters can undergo metabolism to yield trimethylolpropane (2-ethyl-2-hydroxymethyl-1,3-propanediol) and fatty acid constituents. Pentaerythritol and trimethylolpropane have been reported to have a low order of toxicity (Proctor and Hughes, 1996; RTECS 2001; BIBRA, 1987).

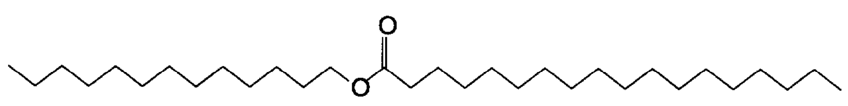
<u>Figure 1 Chemical Structures of Aliphatic Esters</u>
(Note: In some HPV aliphatic esters, there may be possible isomers or the material may be a mixture of components. In general, the chemical structure(s) depicted for each HPV substance represent what is believed to be the predominant isomer or component.

Group A: Aliphatic esters, comprised of monoacids and monoalcohols - " Monoesters"

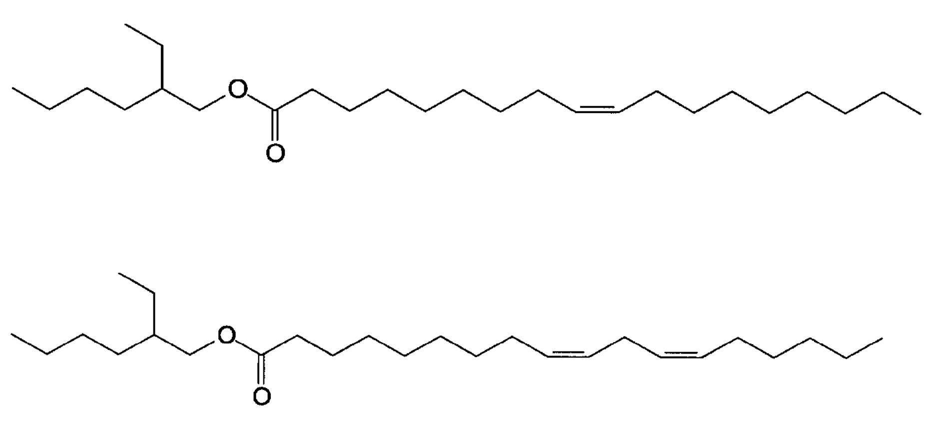
Palmitic acid, 2-ethylhexyl ester (CAS 29806-73-3)



Stearic acid, tridecyl ester (CAS 31556-45-3)

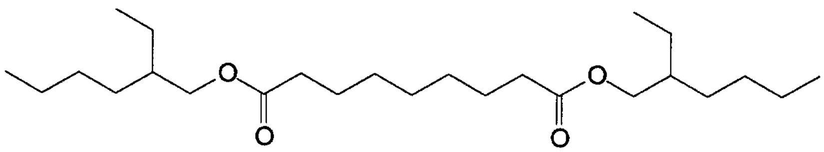


Fatty acids, tall oil, 2-ethylhexyl esters (CAS 68334-13-4)

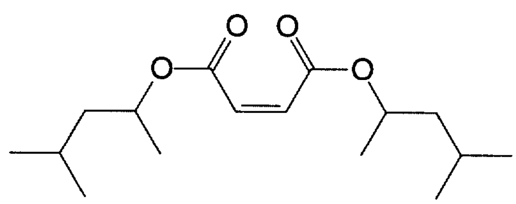


Group B: Aliphatic esters, comprised of diacids and monoalcohols - "Diesters"

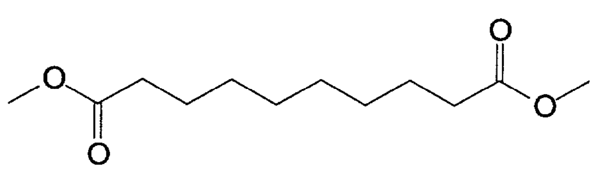
Azelaic acid, bis(2-ethylhexyl)ester (CAS103-24-2)



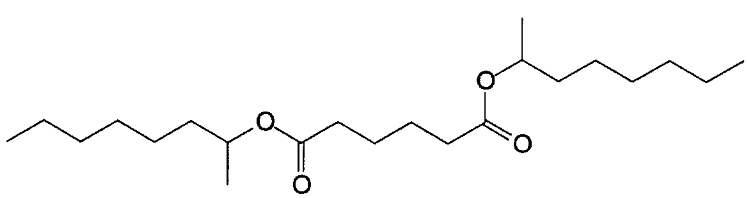
Maleic acid, bis(1,3-dimethylbutyl)ester (CAS 105-52-2)



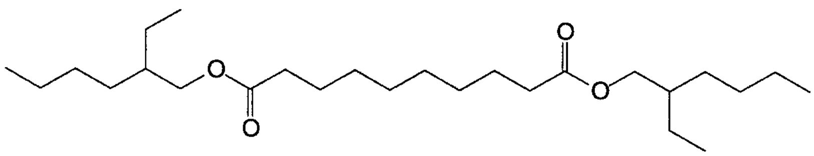
Sebacic acid, dimethyl ester (CAS 106-79-6)



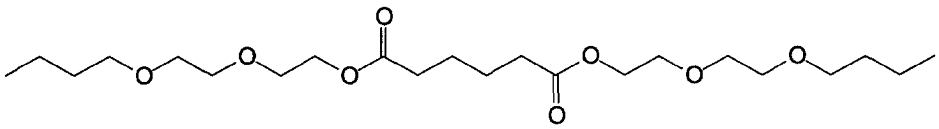
Adipic acid, bis(1-methylheptyl)ester (CAS 108-63-4)



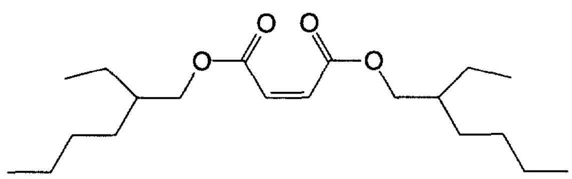
Sebacic acid, bis(2-ethylhexyl)ester (CAS 122-62-3)



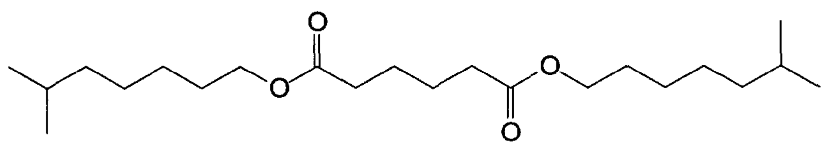
Adipic acid, bis[2-(2-butoxyethoxy)ethyl]ester (CAS 141-17-3)



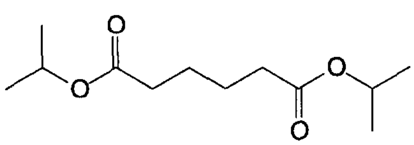
Maleic acid, bis(2-ethylhexyl)ester (CAS 142-16-5)



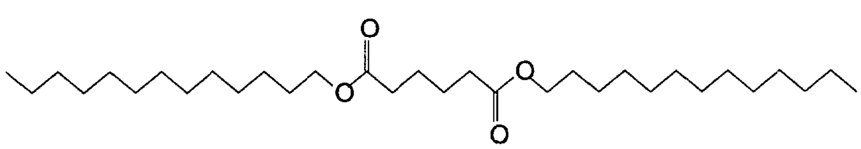
Adipic acid, diisooctyl ester (CAS 1330-86-5)



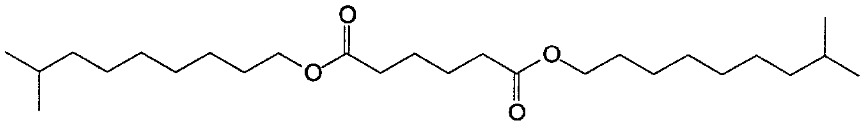
Adipic acid, diisopropyl ester (CAS 6938-94-9)



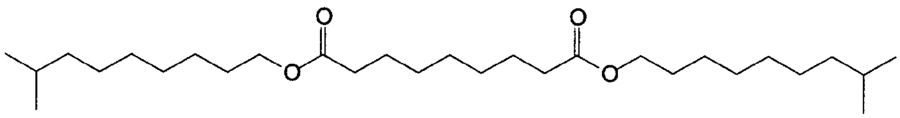
Adipic acid, ditridecyl ester (CAS 16958-92-2)



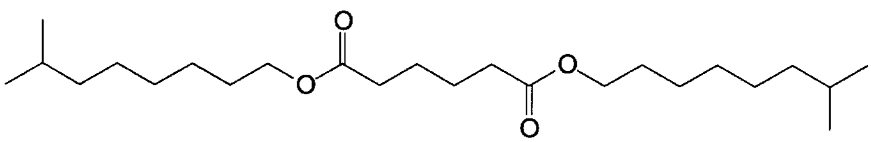
Adipic acid, diisodecyl ester (CAS 27178-16-1)



Azelaic acid, diisodecyl ester (CAS 28472-97-1)

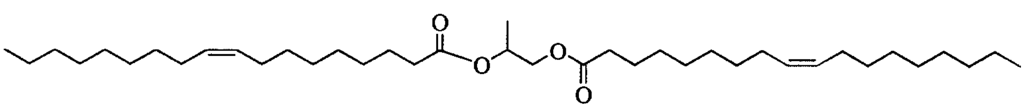


Adipic acid, diisononyl ester (CAS 33703-08-1)

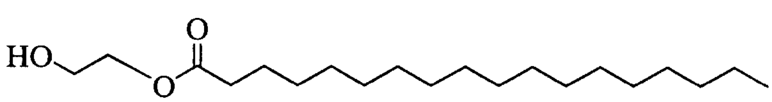


Group C: Aliphatic esters, comprised of monoacids and dihydroxy alcohols - "Glycol Esters"

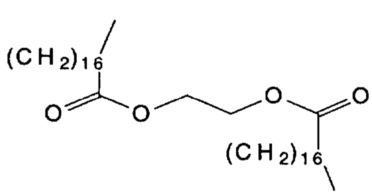
Oleic acid, propylene ester (CAS 105-62-4)



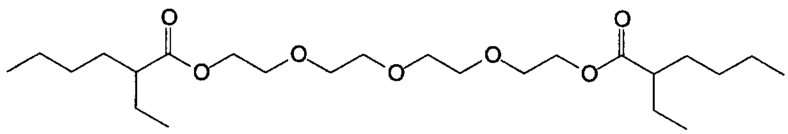
Stearic acid, 2-hydroxyethyl ester (CAS 111-60-4)



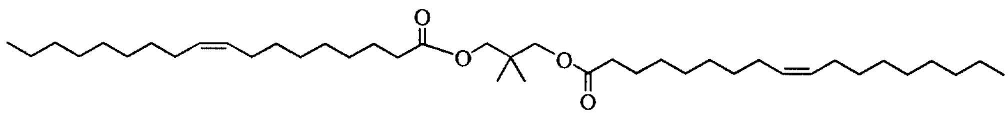
Stearic acid, ethylene ester (CAS 627-83-8)



Hexanoic acid, 2-ethyl-, diester with tetraethylene glycol (CAS 18268-70-7)

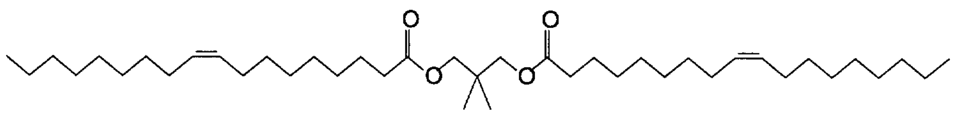


9-Octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediyl ester (CAS 42222-50-4)

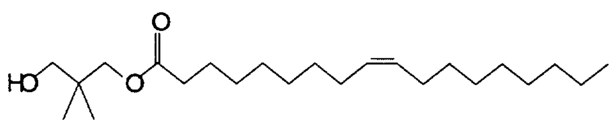


9-Octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol (CAS 67989-24-6)

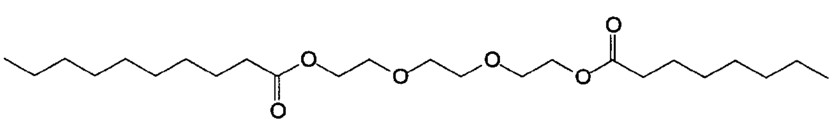
Major (88%)



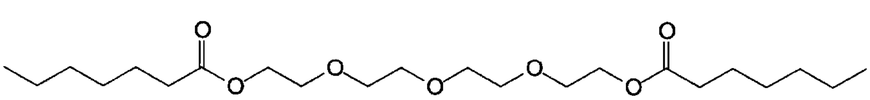
Minor (12%)



Decanoic acid, mixed diesters with octanoic acid and triethylene glycol
(CAS 68583-52-8)

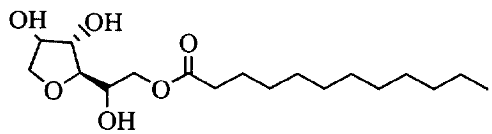


Heptanoic acid, oxybis(2,1-ethanediyloxy-2,1-ethanediyl) ester
(CAS 70729-68-9)

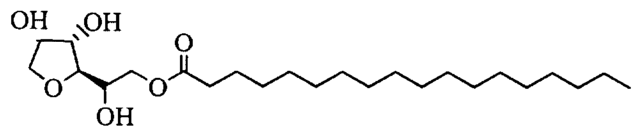


Group D: Aliphatic esters, comprised of monoacids and sorbitan - "Sorbitan Esters"

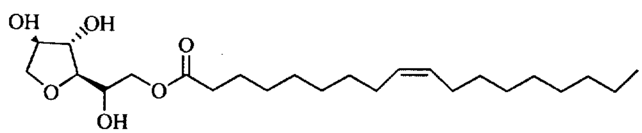
Sorbitan, monolaurate (CAS 1338-39-2)



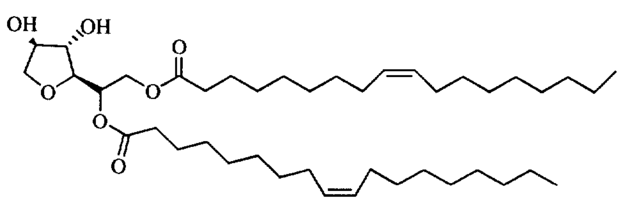
Sorbitan, monostearate (CAS 1338-41-6)

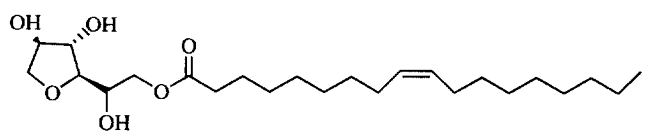


Sorbitan, monooleate (CAS 1338-43-8)

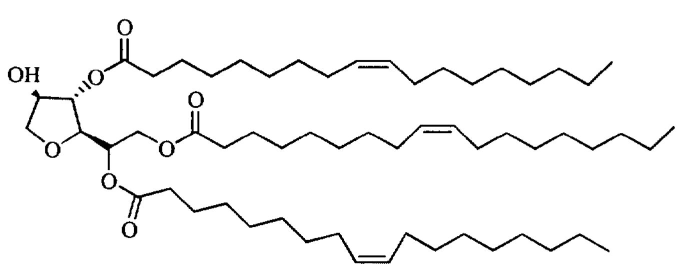


Sorbitan, sesquioleate (CAS 8007-43-0)
is mixture of monooleate and dioleate (~1:1 ratio)

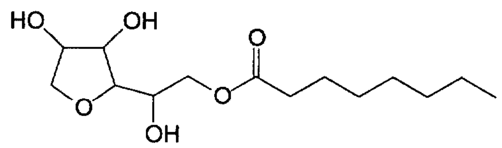


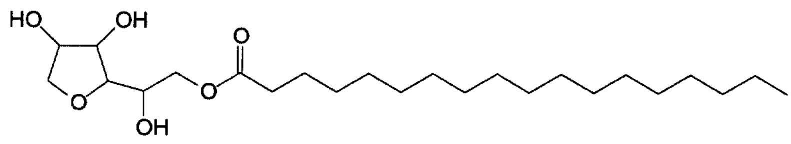


Sorbitan, trioleate (CAS 26266-58-0)



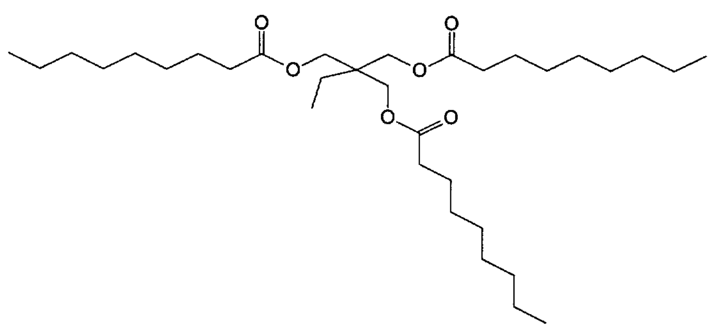
Fatty acids, coco, monoesters with sorbitan (CAS 68154-36-9)



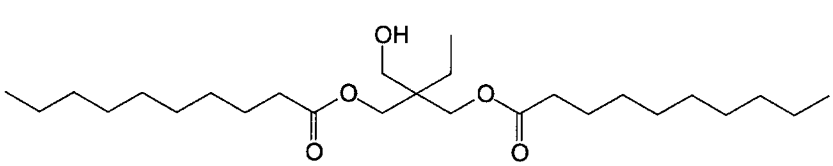


Group E: Aliphatic esters, comprised of monoacids and trihydroxy or polyhydroxy alcohols (polyols) - "Polyol Esters"

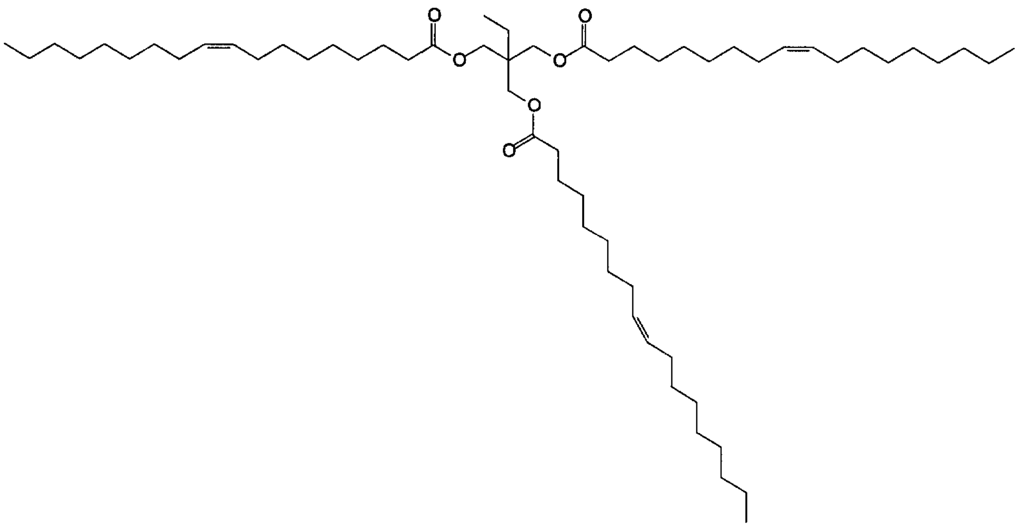
Nonanoic acid, triester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (CAS 126-57-8)



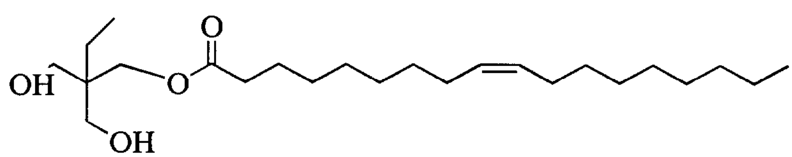
Decanoic acid, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol octanoate
(CAS 11138-60-6)



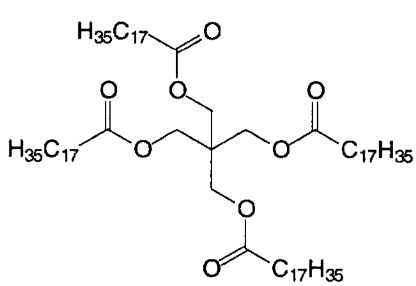
9-Octadecenoic acid (Z)-, 2-ethyl-2-[[(1-oxo-9-octadecenyl)oxy]methyl]-1,3-propanediyl ester, (Z)- (CAS 57675-44-2)



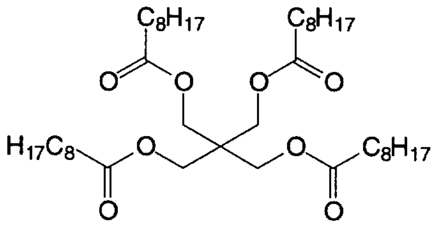
9-Octadecenoic acid (Z)-, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (CAS 70024-57-6)



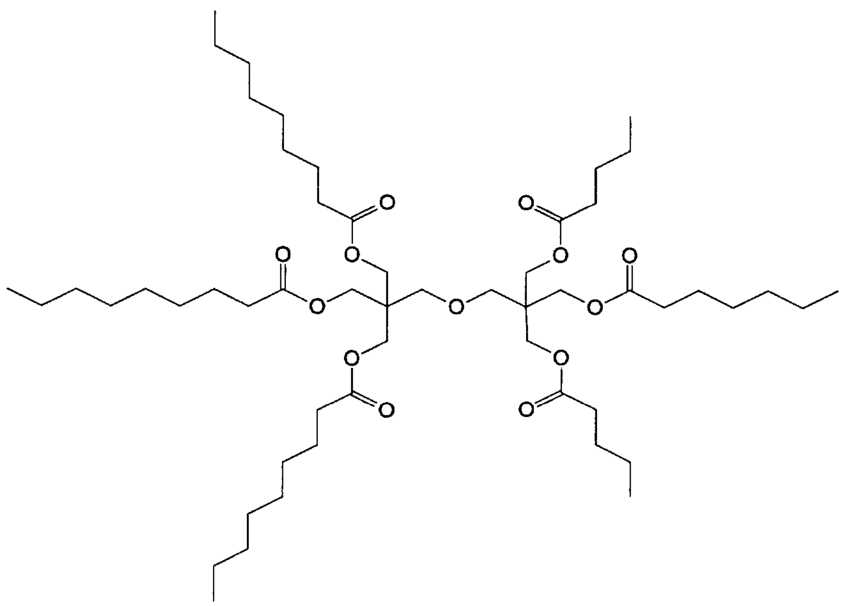
Pentaerythritol, tetrastearate (CAS 115-83-3)



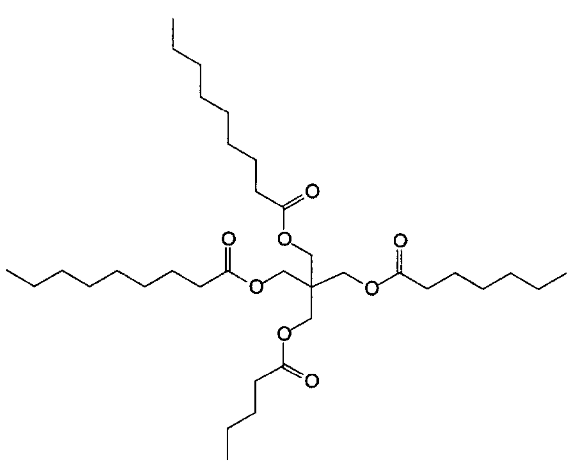
Nonanoic acid, neopentanetetrayl ester (CAS 14450-05-6)



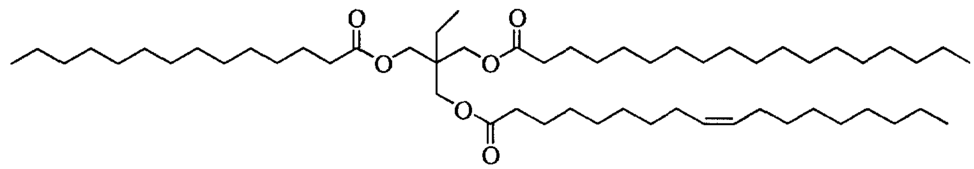
Carboxylic acids, C5-9, hexaesters with dipentaerythritol (CAS 67762-52-1)



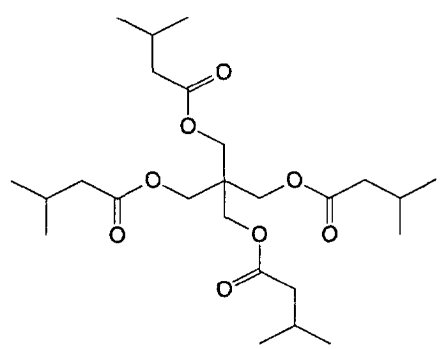
Carboxylic acids, C5-9, tetraesters with pentaerythritol (CAS 67762-53-2)

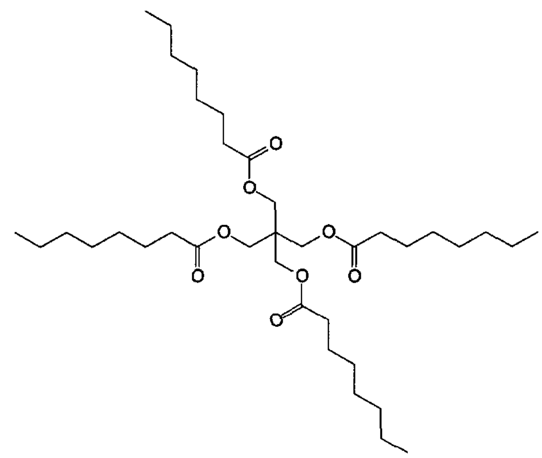


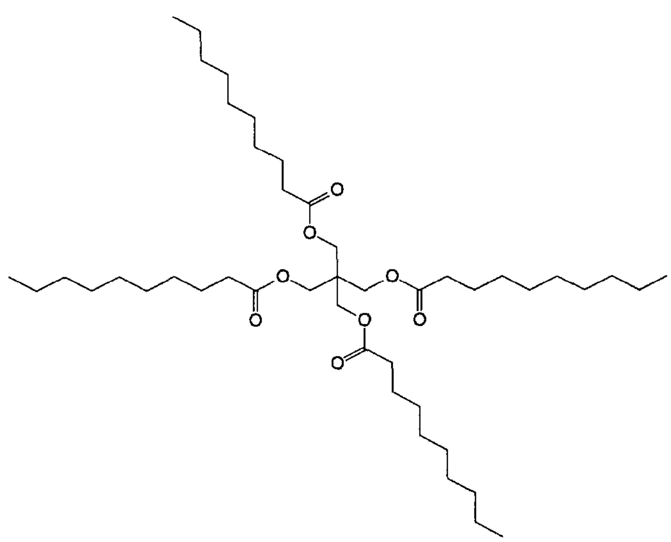
Fatty acids, C14-18 and C16-18 unsatd, triesters with trimethylolpropane (CAS 68002-79-9)



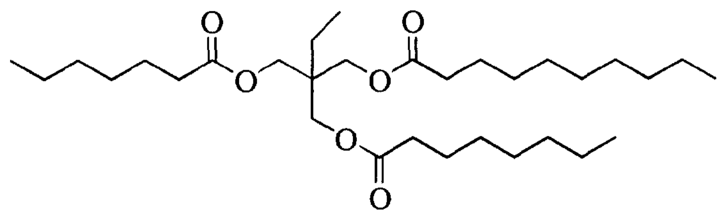
Decanoic acid, mixed esters with heptanoic acid, isovaleric acid, octanoic acid and pentaerythritol (CAS 68130-51-8)



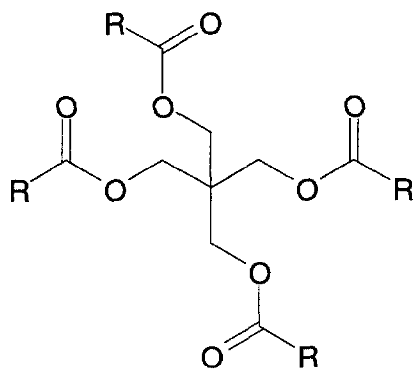




Decanoic acid, mixed esters with heptanoic acid, octanoic acid and trimethylolpropane (CAS 68130-53-0)



Fatty acids, tall oil, tetra esters with pentaerythritol (CAS 68334-18-9)

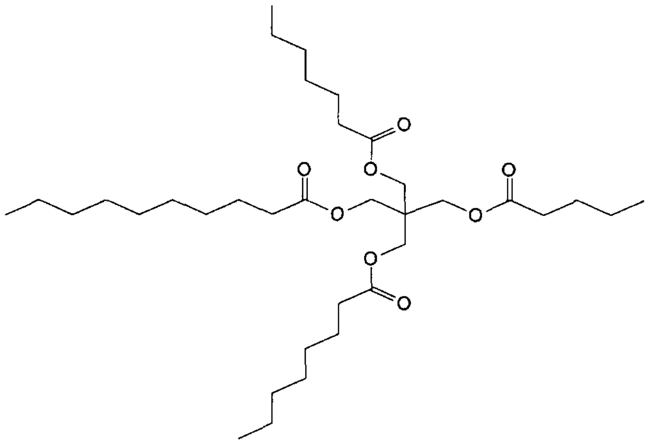


R = predominantly (70-90%) a mixture of

—$(CH_2)_7CH{=}CHCH_2CH{=}CH(CH_2)_4CH_3$ and

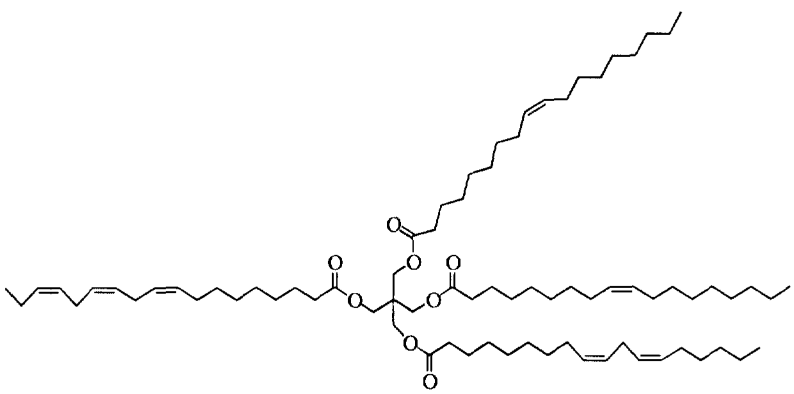
—$(CH_2)_7CH{=}CH(CH_2)_7CH_3$

Fatty acids, C5-10, esters with pentaerythritol (CAS 68424-31-7)

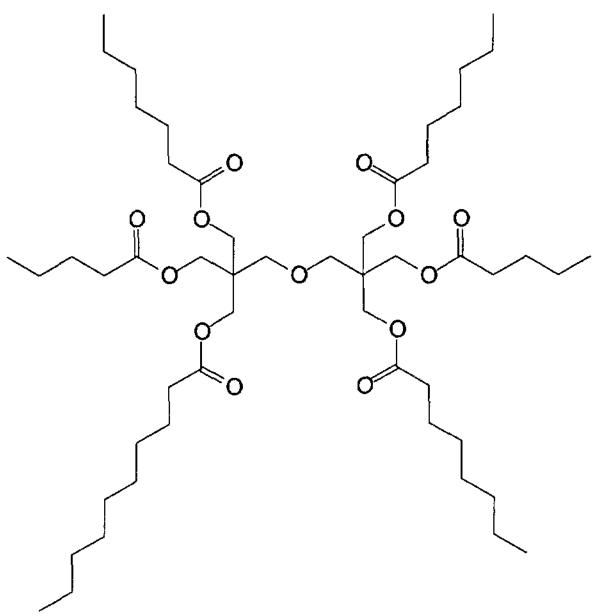


Fatty acids, C5-10, mixed esters with pentaerythritol and valeric acid (CAS 68424-34-0)
--to be added in revised version

Linseed oil, ester with pentaerythritol (CAS 68648-28-2)



Fatty acids, C5-10, esters with dipentaerythritol (CAS 70983-72-1)



3.0 EVALUATION OF AVAILABLE PUBLIC AND COMPANY DATA

A review of the literature and company data was conducted on the physicochemcial properties, environmental fate and effects, and mammalian toxicity endpoints for the 45 aliphatic ester chemicals, using CAS numbers and chemical names. Searches included the following sources: MEDLINE and TOXLINE databases; the TSCATS database for relevant unpublished studies on these chemicals; and standard handbooks and databases (e.g., Sax, CRC Handbook on Chemicals, IUCLID, Merck Index, etc.) for physicochemical properties.

The reports were selected for review based on the following criteria: relevant SIDS endpoint, relevant CAS number, final report of company study (TSCATS), peer reviewed journal, or comprehensive reviews (e.g. Patty's Toxicology, 2001). Several comprehensive safety assessment reviews were found in the literature (i.e., Cosmestic Ingredient Review; J. Amer. College Toxicol.; J. Internat. Toxicol.) for the sorbitan esters, propylene glycol fatty acid esters, adipates and monoesters (e.g., alkyl stearates and oleates). Esters that were chemically or structurally related (e.g., homologs, similar carbon numbers or molecular weight) to the HPV aliphatic esters were reviewed as to whether they were relevant for read-across for environmental fate, aquatic toxicity or mammalian toxicity.

Physicochemical Properties:

Modeled data were entered into the robust summaries for all of the physical properties. There are a number of reasons for this approach:

- The EPA guidance (www.epa.gov/opptintr/chmrtk/robsumgd.htm) allows inclusion of calculated values in the robust summaries for physicochemical elements.
- There was a need for a complete set of physical property data in order to calculate environmental distribution.
- There were data gaps for physical properties for a few of the aliphatic esters.

The physical properties were modeled using the SRI/EPA computer program EPIWIN, a modeling package that includes a number of algorithms developed at or for the EPA. EPIWIN is the program used and advocated by the EPA. Because the model is a structure-property model, a specific discreet structure is required. EPIWIN contains a CAS number database which contains the structures for a large number of chemicals. For mixtures, a single representative structure is contained in the database and in this work, these surrogate chemical structures were accepted for further modeling. It should be remembered that the resultant physicochemical properties are for a single structure and not a mixture so the values are discreet numbers rather than ranges.

Environmental Toxicity:

The environmental data selected for review were primarily obtained through the literature or propietary data. Once the study was identified, a review was performed of the original study document and a robust summary was prepared.

Mammalian Toxicity:

The existing data for the mammalian toxicity endpoints were reviewed using the literature searches to identify the most relevant studies for each chemical in the group. A number of the individual chemicals on the list had no relevant studies identified in the searches. For the listed chemicals that contained relevant data, all available studies were reviewed using the criteria outlined in the EPA's methods for determining the adequacy of existing data for the HPV program and the ranking system proposed by Klimisch et al. (1997). The most relevant studies that were available for the mammalian health endpoints are presented in the Appendices.

Studies that were chosen for robust summaries represented the best available data for a particular SIDS endpoint. Published studies from the general literature, as well as a number of unpublished company reports, were obtained and summarized. Some endpoints include multiple study summaries in order to present a more complete data set. Some of the reported studies (particularly older acute data) could not be summarized because of limited or insufficient experimental detail to assess their quality or only were reported as LD_{50} values from secondary sources. These studies are included in the summary data tables.

4.0 TESTING RATIONALE

Group A - Aliphatic Esters, comprised of Monoacids and Monoalcohols - "Monoesters"

Three HPV aliphatic esters were organized together in Group A because they represent simple "monoesters", comprised of natural fatty acids and a long-chain monoalcohol (2-ethylhexyl and tridecyl alcohol). Six other long alkyl fatty acid esters not on the HPV list were also reviewed because they were structurally related and provided useful data for predicting the toxicity of substances in this group.

The non-HPV long-chain alkyl fatty acid esters were:

- Butyl stearate (CAS 123-95-5),
- Octyl stearate (CAS 109-36-4),
- Decyl oleate (CAS 3687-46-5),
- Myristyl stearate (CAS 17661-50-6),
- Isocetyl stearate (CAS 25339-09-7) and
- Fatty acid, C16-18 saturated and C18 unsaturated, 2-ethylhexyl ester (CAS 85049-37-2).

Physicochemical Properties

The physicochemical properties for the three esters were calculated using EPIWIN and are summarized in Table 2A. Since the three HPV substances are higher fatty acid esters, they would be expected to be rather lipophilic (log Pow 10-14) in character due to the large number of carbon numbers in the ester molecule (e.g., 24, 26, 31 carbons) and they would be expected to have relatively high boiling points. Owing to the non-volatile nature of these esters, their vapor pressures would be expected to be very low and difficult to determine experimentally. Water solubility of the three HPV monoesters was calculated to be very low.

The six non-HPV long-chain alkyl fatty acid esters were also examined and their experimental and calculated (EPIWIN) data also included for comparison. Comparison of the six non-HPV esters indicates that as a general category, most of the alkyl fatty acid esters have high MW (369 to 494), high b.p. (>350°C), high log P (9.7 to 15.5), and very low water solubility.

In addition, hydrolysis half lives and atmospheric photodegradation rates were calculated by EPIWIN. The monoester hydrolysis rates were determined to be quite low and not a significant environmental fate route. Environmental distribution was determined using the EQC (Equilibrium Criterion) model (Mackay, et al. 1996). Fugacity modeling indicates that the fatty acid esters have similar distribution patterns in the environmental compartments (e.g., air, water, soil, sediment) .

On the basis of these results, no additional measurements of the physicochemical or fate properties of the Group A esters are necessary.

Mammalian Toxicity

Acute Toxicity. Available acute toxicity data indicate that the fatty acid esters in Group A, in general, have a low order of toxicity [e.g., palmitic acid, 2-ethylhexyl ester (LD50 > 5 g/kg) and tall oil fatty acid 2-ethylhexyl ester (LD50 > 64 g/kg)]. Consistent with that, available data spanning the carbon range of C22 to C34 indicate that the alkyl fatty acid esters are not toxic by oral administration [rat LD50 (oral) > 5g/kg, with range from 5 g/kg to 64 kg/kg]. Butyl stearate is tolerated by rats without lethal effects at oral doses of 32 g/kg while octyl oleate has a reported LD50 of >40 ml/kg. In addition, many alkyl fatty acid esters, such as the stearates, oleates and palmitates, have been demonstrated to be not toxic by dermal administration (Elders et al. 1982, 1985). Many higher fatty acid esters, such as the stearates, oleates and palmitates, have been cleared for use in the food industry (Bisesi, 2001); thus, their general physiological response and toxicity are very low. Many of the higher fatty acid esters are considered safe for use in cosmetics (Elders, 1985). Because of the low volatility of these substances, inhalation exposure at toxicological significant levels is not expected. Hence, further testing of substances in this group for acute toxicity is not proposed.

Repeated Dose Toxicity. 28-Day oral gavage studies in rats with decyl oleate (CAS 3687-46-5) at doses of 100, 500 and 1000 mg/kg showed no toxicity as noted with respect to clinical symptoms, biochemistry, hematology, gross lesions or tissue/organ histopathology (IUCLID, 1996). The NOAEL was estimated to be 1000 mg/kg. Similarly, octyl or (2-ethylhexyl) stearate showed a NOAEL of 1000 mg/kg in 28-day oral gavage studies in rats. In chronic two-year feeding studies with butyl stearate at concentrations of 1.25% or 6.25% in the diet, exposed rats showed no significant difference from control animals with respect to growth, survival, blood counts or other hematological parameters. Besides the two substances above, various other long-chain fatty acid esters have also been studied for their repeated dose toxicity and the findings support a low order of toxicity (see reviews by Elder, 1982a,b; 1985; Bisesi, 2001). For this reason, further testing of substances in this group for repeated dose toxicity is not necessary.

Genetic Toxicity (Salmonella). Although the HPV esters have not been tested, three of the non-HPV ester surrogates [fatty acid, C16-18 saturated and C18 unsaturated, 2-ethylhexyl ester (CAS 85049-37-2); octyl stearate (CAS 109-36-4); and decyl oleate (CAS 3687-46-5)] were shown to be negative in the Ames assay. Since the monoesters are similar in chemical structure and carbon-number range, it is unlikely that esters in Group A will induce point mutation. In addition, the chemistry of the long-chain fatty acids does not suggest the likelihood that these substances or their constituent substructures (i.e., fatty acids, alcohols) are reactive or electrophilic in nature. Hence, further testing for point mutation is not necessary.

Genetic Toxicity (Chromosomal Aberrations). No information has been reported. As discussed above for point mutation, the chemistry of the long-chain fatty acid esters does not suggest the likelihood that these substances or their constituent substructures (i.e., fatty acids, alcohols) are reactive or electrophilic in nature. Therefore, the likelihood that the fatty acid monoesters may cause chromosomal mutation is very low. A technical discussion document is proposed to address the issue that fatty acid monoesters are not expected to be electrophilic based on their inherent chemistry and therefore, not likely to cause chromosomal aberrations. Thus, no further genetic toxicity testing for chromosomal aberration is proposed for this group.

Toxicity to Reproduction. Assessment of reproductive effects of alkyl fatty acid esters in Group A is based primarily on studies with butyl stearate. Elders (1985) reported that fertility, litter size and survival of offspring were normal in rats fed diets containing 6.25% butyl stearate for 10 weeks. However, growth was reduced in offspring during the pre-weaning and post-weaning periods. No gross lesions were noted among the offspring killed at the end of the 21-day post-weaning periods These results indicate that long-chain fatty acid esters do not cause reproductive toxicity in rats. Given the relative low order of toxicity for long-chain fatty acid esters and their relative non-electrophilic and non-reactive nature, it seems unlikely that the long-chain fatty acid esters would present serious reproductive concerns. Therefore, no further reproductive toxicity testing is proposed for substances in this group.

Developmental Toxicity/Teratogenicity. Assessment of developmental effects for the long-chain fatty acid esters in this group was based primarily on data reported for fatty acid, C16-18, 2-ethylhexyl ester (CAS 91031-48-0). In oral gavage studies in rats administered doses of 100, 300 and 1000 mg/kg during gestation, the maternal NOAEL was > 1000 mg/kg and the NOAEL for teratogenicity was >1000 mg/kg. Based on these findings and the fact that the two HPV substances, palmitic acid, 2-ethylhexyl ester (CAS 29806-73-3) and fatty acid, tall oil, 2-ethylhexyl ester (CAS 68334-13-4), are very chemically similar to the structure of the tested material, fatty acid, C16-18, 2-ethylhexyl ester (CAS 91031-48-0), read-across assessment is appropriate. For this reason, no further testing for developmental toxicity is warranted.

Environmental Toxicity and Biodegradation

Although no ecotoxicity data are available for the three HPV esters, aquatic toxicity results have been reported for two structurally similar alkyl fatty acid esters [i.e., decyl oleate and fatty acid, C16-18 saturated and C18 unsaturated, 2-ethylhexyl ester]. These two non-HPV esters are not acutely toxic to fish (LL50 3200 mg/L). In daphnids, the acute LL50 was reported to be 17 mg/L and in algae, the LL50 was reported to be 40-42 mg/L based on biomass and growth rate endpoints. Because of their limited water solubility, the alkyl fatty acid esters and Group A esters are not likely to cause acute aquatic toxicity. As a consequence, no further aquatic testing is necessary.

Biodegradation of alkyl fatty acid esters are expected to occur extensively based on the reported 28 day test results (80-85% biodegradation, OECD 301D) for decyl oleate and for the 2-ethylhexyl ester of C16-18 saturated and C18 unsaturated fatty acids (CAS 85049-37-2). The HPV esters would be expected to be extensively biodegraded since the fatty acids in these esters are primarily comprised of palmitic, stearic or oleic acids, which are known to be rapidly biodegraded (Verschueren, 1996). Based on the above findings and the chemical similarity of the tested substances with the three HPV substances, no further biodegradability testing is necessary.

Overview

As described earlier, there are three HPV substances organized in Group A. The distinguishing feature of these HPV aliphatic esters is that they represent simple "monoesters", comprised of monocarboxylic acids (ranging from C14-C18, typically natural fatty acids) and simple monoalcohols (ranging from C8-C13). The three HPV aliphatic esters are in the carbon range of C24-C31 and they are very similar structurally to a number of alkyl fatty acid esters that are used extensively in the cosmetic industry [e.g., butyl stearate (CAS 123-95-5), octyl stearate (CAS 109-36-4), decyl oleate (CAS 3687-46-5), myristyl stearate (CAS 17661-50-6), and isocetyl stearate (CAS 25339-09-7)]. There is an adequate database of toxicological information available for these non-HPV long-chain alkyl fatty acid esters. Given the similar chemical/structural features between the three HPV monoesters and the non-HPV alkyl fatty acid esters, this available data would be useful for assessing the Group A substances. Therefore, it is reasonable to presume that the data from the extensively tested alkyl fatty acid esters can be used to predict the toxicological properties of the less studied HPV

Group A chemicals. The chemical structure similarities between the two justify such "read-across" assessments.

Physicochemical properties and environmental fate information are provided in Table 2A. A summary of the available toxicology data is shown in Table 3A. No additional testing is proposed for Group A.

Group A	Acute	Repeat dose	Genetic tox (mutation)	Genetic tox (chrom ab)	Reprod	Develop	Acute fish	Acute daphnia	Algal	Biodeg
Stearic acid, butyl ester *	√	√	R	TD	√	R	R	R	R	R
Palmitic Acid, 2-EH ester	√	R	R	TD	R	R	R	R	R	R
Fatty Acid, tall oil, 2-EH ester	√	R	R	TD	R	R	R	R	R	R
Fatty Acid, C16-18 satd, C18 unsatd, 2-EH esters*	√	R	√	TD	R	√	√	√	√	√
Stearic Acid, octyl ester*	√	√	√	TD	R	√	R	R	R	R
Oleic Acid, decyl ester *	√	√	√	TD	R	R	√	√	√	√
Stearic Acid, tridecyl ester	R	R	R	TD	R	R	R	R	R	R
Stearic Acid, myristyl ester*	√	R	R	TD	R	R	R	R	R	R
Stearic Acid, isocetyl ester*	√	R	R	TD	R	R	R	R	R	R

* Not U.S. HPV aliphatic ester; data included for read-across to other group category members
The clinical safety of many of the non-HPV alkyl fatty acid esters have been extensively reviewed by the Cosmetic Ingredient Review Expert Panel (see Elder 1982a,b; 1985).

Abbreviations in table: √ = adequate data; R = read-across, TD = Technical Discussion Proposed

Group B - Aliphatic Esters, comprised of Diacids and Monoalcohols - "Diesters"

Thirteen HPV alipatic esters were organized in Group B. These substances were grouped together since they are structurally related "diesters" derived from common organic diacids such as adipic, maleic, azelaic and sebacic acids. In addition, many of the diesters fell within the carbon range of C22-C32 and had similar properties and structural characteristics. Four other diesters, not on the HPV list, were also reviewed because they were structurally similar and provided useful data for bridging toxicity information and for assessing (i.e., read-across) the health effects of the aliphatic esters in this group.

The four non-HPV diesters are:

- Maleic acid, dibutyl ester (CAS 105-76-0)
- Adipic acid, dibutyl ester (CAS 105-99-7)
- Adipic acid, di-C7-9 branched and linear alkyl ester (CAS 68515-75-3)
- Adipic acid, bis(2-ethylhexyl) ester (CAS 103-23-1).

Physicochemical Properties

There is a significant amount of reported experimental data for the physicochemical properties of the esters in Group B, especially the adipates (Table 2B). Computer models were also used to estimate these properties for comparison with measured values and to help predict the environmental distribution of the HPV Group B diesters and the three non-HPV adipates. The calculated data were developed using EPIWIN, a computer model that the EPA has cited for use in the HPV Challenge Program.

In general, the short-chain alkyl (e.g., methyl, isopropyl, and butyl) diesters were generally more water soluble, less lipophilic and relatively more volatile than the corresponding long-chain alkyl (C7-C13 alcohol) diesters. However, most of the diesters on the HPV list (10 of 13) have molecular weight of greater than 350, have high boiling points (>300°C) and are expected to be relatively non-volatile, lipophilic (log P > 7) and extremely water-insoluble.

The distribution between the environmental compartments for Group B diesters is influenced by the water solubility and lipophilicity. In general, for diesters with higher water solubility characteristics (e.g., diisopropyl adipate and dibutyl adipate, dimethyl sebacate), the EQC models (Mackay et al., 1996) predicted a greater distribution of the test substance in the water compartment. For more lipophilic diesters, the EQC models predicted a greater distribution in soil and sediment. Hydrolysis half-lives and atmospheric photodegradation rates were calculated using EPIWIN and are summarized in the table.

Sufficient physicochemical data exist for the Group B diesters and no additional testing is needed.

Mammalian Toxicity

Acute Toxicity. Acute toxicity data, showing a low order of toxicity, have been reported for 11 of the 13 HPV esters in Group B. Oral rat LD50 values ranged from >2 g/kg to >64 g/kg. Acute oral toxicity data have also been reported for the non-HPV substances. Further testing of substances in this group for acute toxicity is not necessary.

Repeated Dose Toxicity. Data on repeated dose toxicity have been reported for diisononyl adipate and tridecyl adipate. In 90-day toxicity studies, rats were administered diisononyl adipate (CAS 33703-08-1) in the diet at levels equivalent to 0, 50, 150 and 500 mg/kg/day. The NOAEL was 500 mg/kg/day. Feeding studies were also carried out in beagle dogs for 13 weeks at dietary concentrations of 0, 0.3, 1 and 3% (increased to 6% at week 9). The NOAEL was determined to be 1% in the diet or approximately 274 mg/kg/day. In another 13-week study, ditridecyl adipate was well tolerated in rats given dermal doses of 800 and 2000 mg/kg/day.

In addition, 90-day subchronic dietary studies have been carried out with two non-HPV adipates: namely, adipic acid di-C7-9 branched and linear alkyl ester (CAS 68515-75-3) and adipic acid, bis(2-ethylhexyl) ester (CAS 103-23-1). For adipic acid di-C7-9 branched and linear alkyl ester (CAS 68515-75-3), rats were fed 0, 0.1, 0.5 and 2.5% of the test substance in the diet. No significant signs of toxicity were observed in male and female rats administered the test material in the diet at concentrations up to 2.5% for a period of 13 weeks. The NOAEL was 2.5% for both sexes (males ~1300 mg/kg; females ~1800 mg/kg). In the 90-day dietary studies with 2-ethylhexyl adipate (CAS 103-23-1), the NOAEL was ~300 mg/kg/day in rats and ~230 mg/kg/day in mice. The LOAEL was ~600 mg/kg/day in rats and ~460 mg/kg/day in mice. Hepatic hypertrophy and increased peroxisomal enzyme activity occurred in rats and mice; however, there were no adverse effects on the liver. Repeated oral gavage studies (7-day) have been reported also for dibutyl maleate (Table 3B).

Sufficient subchronic toxicity data exist for diesters in the C12-C32 carbon range, from the studies carried out to date. Therefore, there is no need to carry out additional repeated dose toxicity studies of substances in Group B.

Genetic Toxicity (Salmonella). Three HPV substances [i.e., adipic acid ditridecyl ester, adipic acid diisononyl ester and sebacic acid bis(2-ethylhexyl) ester] were shown to be negative in the Ames assay. In addition, diisononyl adipate was negative in the mouse lymphoma assay. Adipic acid, bis(2-ethylhexyl) ester (non-HPV) has also been evaluated for mutagenicity and was found to be negative in both the Ames and mouse lymphoma assays. Although the two maleate diesters have not been tested, it has been reported that dibutyl maleate (CAS 105-76-0) is negative in the Ames assay (Table 3B). As all of these diesters were inactive for mutagenicity, further testing of Group B diesters for point mutation is not warranted.

Genetic Toxicity (Chromosomal Aberrations). Adipic acid, ditridecyl ester (CAS 16958-92-2) was negative in the micronucleus assay. The non-HPV substance, adipic acid bis(2-ethylhexyl) ester (CAS 103-23-1), also did not cause chromosomal aberrations in the Chinese hamster ovary cell assay or the mouse micronucleus test (David et al. 2001). Since these two adipates cover the carbon number range of C22-C32 for the diesters, it is unlikely that the substances in Group B are chromosomal mutagens. In addition, dibutyl maleate (C12) has been shown to be negative in the mouse micronucleus test in vivo. Therefore, no further testing for chromosomal aberrations is proposed for this group.

Toxicity to Reproduction. Di-2-ethylhexyl adipate (DEHA)(CAS 103-23-1) has been evaluated for reproductive effects in a one-generation study. Male and female rats were administered DEHA in their diets at same levels (0, 28, 170 or 1080 mg/kg/day). After 10 weeks on the diet, the animals were mated to produce one generation of offspring. Test diets were fed continuously throughout the study (18-19 weeks of exposure). No effects were seen on male or female fertility. However, at the highest dose, there was a reduction in body weight in the dams, and reduction in offspring body weight, total litter weight and litter size. The NOAEL and LOAEL for this study was 170 and 1080 mg/kg/day, respectively (ICI, 1988a). In 13-week dermal studies with ditridecyl adipate, there was no sperm morphological changes observed in male rats treated at levels of 2000 mg/kg. Increases in organ weight of the epididymides and uterus were observed at dermal exposure to 2000 mg/kg but not at 800 mg/kg. In a 19-week oral feeding study with sebacic acid, bis(2-ethylhexyl) ester (CAS 122-62-3), no adverse reproductive effects were reported for this material (BIBRA, 1996). Dibutyl maleate has been evaluated in an OECD reproductive/developmental toxicity screening test (oral gavage) and no adverse effects on reproduction were reported (OECD SIDS dossier for dibutyl maleate). Since these four materials cover the carbon number range of C12-C32 for the diesters and because of the chemical similarity of the alkyl diesters, the available reproductive toxicity data should be sufficient for read-across assessment of most of the other diesters in Group B. Therefore, no additional testing for reproductive toxicity is necessary for this group.

Developmental Toxicity/Teratogenicity. Developmental studies have been carried out with three non-HPV diesters. No evidence of developmental toxicity was observed at dose levels of 1000 and 4000 mg/kg/day after oral gavage of adipic acid, di-C7-9 branched and linear alkyl ester (CAS 68515-75-3). Slight maternal toxicity (reduced body weight) and embryotoxicity (reduced fetal weight) was observed at the highest dose (7000 mg/kg/day). The NOAEL for maternal and developmental toxicity was 4000 mg/kg/day. No adverse developmental effects were reported for dibutyl maleate in an OECD reproductive/developmental screening study.

The developmental toxicity has also been evaluated for adipic acid, bis(2-ethylhexyl) ester (CAS 103-23-1) by dietary exposure. Pregnant rats administered 2-ethylhexyl adipate in the diet throughout gestation showed reduced body weight at dietary equivalent doses of 1080 mg/kg/day. At 1080 mg/kg/day, implantation fetal loss was evident; however, no gross, skeletal or visceral abnormalities were observed. LOAEL was 1080 mg/kg/day and NOAEL was 170 mg/kg/day (developmental toxicity)(ICI, 1988b). The developmental toxicity data from these three studies provide sufficient data for the read-across assessment of most of the other diesters in Group B due to their chemical structural similarities. Therefore, no further developmental toxicity testing is proposed.

Environmental Toxicity and Biodegradation

Acute aquatic toxicity studies have been carried out with five of the HPV diesters and three of the non-HPV adipates. There is sufficient information on the toxicity data in fish, invertebrates and algae for many of the Group B aliphatic esters (Table 3B). The diesters included maleates, adipates, azelates and sebacates in the carbon range of C12-C32, which basically bridges most of the 13 diesters.

In general, the tested diesters did not cause acute toxicity to aquatic organisms. Since the long-chain length diesters have very limited water solubility, these materials are probably not likely to cause toxicity at their maximum water solubility. For example, no mortality was reported in fish, daphnia and algae at water saturation levels for 2-ethylhexyl adipate. Since the matrix set of available aquatic toxicity data provides sufficient information for read-across assessment of most of the other diesters in Group B, no further aquatic toxicity testing is needed.

Biodegradability results have been reported for seven of the 13 HPV diesters as well as for the non-HPV diesters. Most of the tested diesters were readily biodegradable which indicates that long-chain diesters are capable of undergoing very extensive biodegradation in aqueous aerobic environments. Although there are differences in the overall percent biodegradation among the diesters, this is not unexpected given potential structural differences (e.g., degree of branching in alcohol portion of molecule) and given water solubility limitations for many of the diesters. Regardless, the information available for the matrix set indicates that diesters are extensively biodegraded. Dimethyl maleate and dibutyl maleate have been reported to undergo rapid biodegradation (>95% in 28 days) (IUCLID, 1996; OECD SIDS dossier for dibutyl maleate). Therefore, short-chain alkyl diesters such as diisopropyl and dibutyl adipates and dimethyl sebacate would also be expected to be biodegraded to a similar extent. Since there are sufficient experimental data reported, which covered the range of diesters on the HPV list, no additional biodegradability testing is necessary.

Overview

As discussed earlier, thirteen HPV aliphatic esters were organized into Group B. The distinguishing chemical feature of this group of substances is that they are ester derivatives of the common diacids: namely, maleic (C4), adipic (C6), azelaic (C9) and sebacic (C10) acids. The alcohol portion in most of the diesters falls in the C7-C13 carbon number range and they typically have branched structural features. Ten of the 13 HPV diesters fall in the C20-C32 carbon range; for this reason, most of the diesters have high boiling points, low volatility, low water-solubility and high lipophilic characteristics. The shorter-chain alkyl diesters (e.g., dimethyl sebacate, diisopropyl and dibutyl adipates) have greater water solubility, greater volatility and lower lipophilicity than the corresponding long-chain (C7-C13) alkyl diesters.

Other non-HPV diesters, especially maleic acid, dibutyl ester; adipic acid, di-C7-9 branched and linear alkyl ester; and adipic acid, bis(2-ethylhexyl) ester, have been extensively tested. They are included in this review mainly because they provide useful toxicological data for assessing the Group B substances. Collectively, the seven HPV adipates and the three non-HPV adipates represented a broad homologous series of diesters that was useful in the matrix analysis of the HPV substances. The chemical structure similarities among the diesters justify grouping these substances together on toxicological grounds. The physicochemical, environmental and toxicological data from the HPV and the non-HPV materials cover the majority of carbon numbers in the diesters in Group B.

Physicochemical properties and environmental fate information are provided in Table 2B. A summary of the available toxicology data is shown in Table 3B. No additional testing is proposed for Group B.

Group B	Acute	Repeat dose	Genetic tox (mutation)	Genetic tox (chrom ab)	Reprod	Develop	Acute fish	Acute daphnia	Algal	Biodeg
Maleic acid, dibutyl ester *	√	√	√	√	√	√	√	√	√	√
Maleic acid, bis(1,3-dimethylbutyl)ester	√	R	R	R	R	R	R	R	R	R
Maleic acid, bis(2-ethylhexyl)ester	√	R	R	R	R	R	R	R	R	R
Adipic acid, diisopropyl ester	√	R	R	R	R	R	R	R	R	R
Adipic acid, dibutyl ester *	√	R	R	R	R	R	R	R	R	R
Adipic acid, di-C7-9 branch and linear alkyl esters*	√	√	√	R	R	√	√	√	√	R
Adipic acid, diisooctyl ester	√	R	R	R	R	R	R	R	R	√
Adipic acid, bis(1-methylheptyl)ester	√	R	R	R	R	R	R	R	R	R
Adipic acid, bis(2-ethylhexyl)ester*	√	√	√	√	√	√	√	√	√	√
Adipic acid, bis[2-(2-butoxyethoxy)ethyl]ester	R	R	R	R	R	R	R	R	R	R
Adipic acid, diisononyl ester	√	√	√	R	R	R	√	R	R	√
Adipic acid, diisodecyl ester	√	R	R	R	R	R	R	R	R	√
Adipic acid, ditridecyl ester	√	√	√	√	√	R	√	√	R	√
Azelaic acid, bis(2-ethylhexyl)ester	√	R	R	R	R	R	√	R	R	√
Azelaic acid, diisodecyl ester	√	R	R	R	R	R	√	R	R	√
Sebacic acid, dimethyl ester	R	R	R	R	R	R	R	R	R	R
Sebacic acid, bis(2-ethylhexyl)ester	√	√	√	R	√	R	√	√	√	√

* Not U.S. HPV aliphatic ester; data included for read-across to other group category members
Abbreviations in table: √ = adequate data; R = read-across

Group C - Aliphatic Esters, comprised of Monoacids and Dihydroxy Alcohols - "Glycol Esters"

Eight HPV aliphatic esters were classified in Group C based on the presence of the diol or glycol functionality which was common to all these "glycol esters". The HPV substances were ester derivatives (e.g., C6-C18 fatty acids) of, mainly, ethylene glycols or propylene glycols. Five non-HPV glycol or diol esters were also reviewed because they were chemically similar and provided useful data for bridging the toxicity of substances in this group.

The five non-HPV glycol esters were:

- Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (CAS 71839-38-8)
- Triethylene glycol, diheptanoate (CAS 7434-40-4)
- Propylene glycol, monostearate (CAS 1323-39-3)
- Propylene glycol, dilaurate (CAS 22788-19-8)
- Propylene glycol, diisostearate (CAS 68958-54-3)

Physicochemical Properties

The experimental and calculated physicochemical properties for the "glycol esters" in Group C are summarized in Table 2C. EPIWIN was used to estimate these properties for comparison with measured values and to help predict the environmental distribution in the various compartments.

In general, the glycol monoesters with shorter carbon-number fatty acids (C7) were more water-soluble and less lipophilic than the corresponding glycol monoesters containing long-chain fatty acids such as stearic and oleic acids. The glycol diesters were predicted to be more lipophilic and less water-soluble than the corresponding glycol monoesters (e.g., ethylene glycol monostearate *versus* distearate; propylene glycol monooleate *versus* dioleate). In addition, the glycol diesters have higher boiling points than the corresponding monoesters.

Polyglycol esters, that contain more than one repeating ethylene glycol unit, generally showed greater water solubility than the corresponding monoglycol esters, owing to the increased polarity of multiple ether linkages; this was consistent with what would be expected. The greater degree of ether linkage was also consistent with the lower lipophilicity (log P) values predicted by EPIWIN.

Most of the glycol esters on the HPV list have molecular weights of greater than 300, have high boiling points (>400 C) and showed low water solubility and high lipophilic characteristics (log P >5). The glycol distearates and dioleates had carbon numbers above C38 and high boiling points (>550 °C).

In additon, hydrolysis half lives and atmospheric photodegradation rates were calculated using EPIWIN. Environmental distribution was determined using EQC.

No further measurements of physicochemical properties or fate are needed for this group.

Mammalian Toxicity

Acute Toxicity. The available data indicate the HPV glycol esters have a low order of acute toxicity by the oral administration. The reported oral rat LD50 values ranged from 2g/kg to 34.6 g/kg. Four of the eight HPV glycol esters in Group C have been tested. In addition, acute toxicity data have been reported for many other non-HPV glycol esters. In particular, the ethylene glycol and propylene glycol esters have been extensively studied and their health safety evaluated (Andersen, 1999; Elder, 1982c, 1983). For example, propylene glycol monostearate (CAS 1323-39-3) has an acute oral LD50 of 25.8 g/kg in rats. Propylene glycol stearate has been approved for a variety of pharmaceutical uses and is considered Generally Recognized as Safe (GRAS) for food or food contact use (Elder, 1983). Hence, further testing of substances in this group for acute toxicity is not proposed.

Repeated Dose Toxicity. Subchronic studies have been carried out with heptanoic acid, oxybis[2,1-ethanediyloxy-2,1-ethanediyl] ester (CAS 70729-68-9). In 28-day oral gavage studies in rats, the NOAEL was determined to be 1000 mg/kg. No signs of toxicity were observed and no treatment-related changes in hematology or clinical chemistry were reported.

Two non-HPV glycol esters have also been evaluated in repeated dose toxicity studies. Propylene glycol monostearate (CAS 1323-39-3), which was administered for 13 weeks at dietary concentrations of 0, 1.5%, 3.36% and 7.52%, showed no signs of toxicity in rats. Similarly, in 6-month oral studies, no signs of toxicity, gross or histological pathology were observed in rats and dogs fed diets containing up to 10% propylene glycol stearate (Elder, 1983). For another non-HPV glycol ester, heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (CAS 71839-38-8), doses up to 1000 mg/kg/day were well tolerated in rats that were orally (gavage) administered the test material for 28 days. Signs of toxicity were either minor, reversible or sex/species specific. Increased liver weights observed at 1000 mg/kg dose are believed to be associated with adaptive changes associated with metabolism (e.g., enzyme induction) and not toxicity as such. Hyaline droplet formation observed in the male kidneys is believed to be a sex/species condition specific to only male rats, which has little relevance to humans.

The findings from the studies above as well as other subchronic dermal toxicity studies for other propylene glycol monoesters and diesters (Elder 1982c, 1983; Johnson, 1999) indicate that there are sufficient data on the repeated dose toxicity of the glycol esters available to provide read-across assessments. Thus, no additional testing for repeated dose toxicity for substances in this group is warranted.

Genetic Toxicity (Salmonella). One HPV substance, heptanoic acid, oxybis[2,1-ethanediyloxy-2,1-ethanediyl] ester (CAS 70729-68-9), has been shown to be negative in the Ames assay. In addition, three non-HPV glycol esters [heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol; triethylene glycol diheptanoate; and propylene glycol monostearate] have been found to be negative in the Ames test as well. These findings indicate that the glycol esters do not cause point mutations. This is consistent with the chemistry of the glycol esters, which does not suggest the likelihood that these substances, or their constituent glycols or fatty acids, are electrophilic or reactive in nature. Therefore, no additional testing for point mutation for substances in this group is warranted.

Genetic Toxicity (Chromosomal Aberrations). Heptanoic acid, oxybis[2,1-ethanediyloxy-2,1-ethanediyl] ester (CAS 70729-68-9) has been evaluated and did not cause chromosomal aberrations in the Chinese hamster ovary cell assay. In addition, the non-HPV substance, heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (CAS 71839-38-8), has also been evaluated in the *in vitro* cytogenetics test using human peripheral lymphocytes. It showed negative results for chromosomal aberrations. The available information on these two substances indicates that glycol esters are not likely to cause chromosomal aberrations. This is consistent with the chemistry of the glycol esters, which does not suggest the likelihood that these substances, or their constituent glycols or fatty acids, are electrophilic or reactive in nature. Therefore, the likelihood that the glycol esters may cause chromosomal aberration is very low. For these reasons, no further genetic toxicity testing for chromosomal aberration is necessary.

Toxicity to Reproduction. No information has been reported. However, recent comments by the Cosmetic Ingredient Review expert panel on the reproductive hazard assessments of polyethyleneglycol ethers may have particular significance and implications in the context of assessing the reproductive and developmental toxicity of the glycol esters. This panel clearly pointed out that the polyethylene diesters are chemically different from the polyethylene glycol monoalkyl ethers (Andersen, 1999). The glycol diesters do not give rise to methoxyethanol or ethoxyethanol, metabolic products which have been implicated in the reproductive and developmental toxicity associated with the polyethylene glycol ethers. These metabolites of concern arise from metabolism of the ethylene glycol monoalkyl ethers and are not expected to be produced metabolically from polymers of ethylene glycol or their ester derivatives. This suggests that reproductive/developmental toxicity concerns would not exist for the glycol diesters/monoesters in the same manner that they do for the glycol monoalkyl ethers. These distinctive differences in the chemistry and metabolism between the glycol esters and polyethylene glycol ethers need to be highlighted and emphasized in the context of reproductive and developmental toxicity. A technical discussion document will be developed to address the reproductive/developmental toxicity issue for the glycol esters in that they are not likely to cause reproductive toxicity.

Developmental Toxicity/Teratogenicity. No information has been reported. However, as discussed for reproductive toxicity, the glycol diesters are not expected to give rise to methoxyethanol or ethoxyethanol, metabolic products which have been implicated in the reproductive and developmental toxicity associated with the polyethylene glycol ethers. This suggests that reproductive/developmental toxicity concerns would not exist for the glycol esters in the same manner that they do for the glycol monoalkyl ethers. These distinctive differences in the chemistry and metabolism between the glycol esters and polyethylene glycol ethers need to be highlighted and emphasized in the context of reproductive and developmental toxicity. A technical discussion document will be developed to address the developmental toxicity issue for the glycol esters in that they are not likely to cause reproductive/ developmental toxicity.

Additional note: Johnson (1999) carried out an excellent and comprehensive safety assessment of thirteen propylene glycol esters (fatty acid C8 to C18), which not only evaluated the health effects of the glycol esters but also highlighted the non-toxicity of propylene glycol and the individual fatty acids [e.g., stearic, oleic, lauric, myristic, and caprylic/capric (C10/C9)]. It appears from this assessment that propylene glycol and the fatty acids have low orders of reproductive/developmental toxicity.

Environmental Toxicity and Biodegradation

Acute toxicity data in fish, daphnia or algae have been reported for several glycol esters including: triethylene glycol diheptanoate (CAS 7434-40-4), heptanoic acid, oxybis[2,1-ethanediyloxy-2,1-ethanediyl] ester (CAS 70729-68-9) and the oleate ester with 2,2-dimethyl-1,3-propanediol (CAS 67989-24-6). The available ecotoxicity data indicate that these glycol esters, in general, are not toxic to aquatic organisms. While the higher molecular weight glycol esters (>C38, MW 500) have not been evaluated, they are expected to be relatively non-toxic as a result of their very poor water solubility and the fact that many of the HPV substances are simply the diester homolog of the corresponding glycol monoesters. For example, 9-octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediyl (di)ester (CAS 4222-50-4) is simply the diester of 9-octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol (CAS 67989-24-6). The latter (i.e., monoester) has been tested and shown to be non-toxic to daphnids (LL50 ~2000 ppm). Enzymatic cleavage of the ester linkage in the diester (CAS 4222-50-4) would yield the corresponding monoester and oleic acid, both of which are not toxic to aquatic organisms. It is of interest to note that ethylene glycol and propylene glycol are not acutely toxic to aquatic organisms (Verschueren, 1996; IUCLID 1996). In addition, fatty acids (e.g., stearic and oleic acids) that may be generated from enzymatic metabolism of the glycol esters are expected to have a low order of aquatic toxicity. Hence, there are sufficient data available to allow for read-across assessment of the glycol esters and no further aquatic testing is proposed for the Group C substances.

Biodegradation studies with two HPV and two non-HPV glycol esters have been reported. These results indicate that the glycol esters are readily biodegradable. The extent of biodegradation has been reported to range from 65% to 98% in 28 days for the four glycol esters. The tested substances covered the C15-C23 carbon range for the glycol esters. Glycol esters above C30 are mainly comprised of the glycol diesters such as the dioleates and distearates, and several of the HPV substances are simply the diester homolog of the corresponding monooleate or monostearate esters. These diesters are expected to be metabolized to the corresponding monoesters, which have been demonstrated to be readily biodegradable.

Enzymatic breakdown products of the glycol esters, such as propylene glycol, ethylene glycol and their fatty acids, have been reported to be readily biodegradable (Swisher, 1987; Vershueren, 1996; IUCLID 1996). In summary, it is expected that most of the HPV glycol esters would be rapidly and extensively biodegraded in the environment. Further biodegradation testing for substances in this group is not necessary given the sufficient amount of data available for assessing the biodegradability potential of structurally similar glycol esters.

Overview

As discussed previously, eight HPV aliphatic esters have been assigned to Group C . The distinguishing chemical feature of this group of substances is that they are ester derivatives of ethylene glycol and propylene glycol (the alcohol portion of the ester molecule). Fatty acids (C6-C18) make up the carboxylic acid portion of the ester molecule, with oleic and stearic acids being the most common. The HPV glycol esters cover the C20-C40 carbon number range and most have molecular weights of greater than 300, have high boiling points (>400°C) and showed low water solubility and high lipophilic characteristics. However, available data indicate that glycol esters undergo very extensive biodegradation and they are not acutely toxic to aquatic species.

The common occurrence of the ethylene glycol or propylene glycol substructure and natural fatty acids like oleic and stearic acid justify grouping the HPV glycol esters on toxicological grounds. Additionally, many non-HPV glycol esters, such as propylene glycol stearates, oleates and laurates, which are commonly used in many cosmetics, are remarkably similar in structure to the HPV substances in Group C. It is noteworthy that propylene glycol stearate has been approved for a variety of pharmaceutical applications and is "Generally Recognized as Safe" (GRAS) for food use (Elder, 1983). Therefore, the non-HPV glycol esters included in this review were useful in providing data to help assess the toxicity of other less studied members of this group.

Physicochemical properties and environmental fate information are provided in Table 2C. A summary of the available toxicology data is shown in Table 3C. No additional testing is proposed for Group C.

Group C	Acute	Repeat dose	Genetic tox (mutation)	Genetic tox (chrom ab)	Reprod	Develop	Acute fish	Acute daphnia	Algal	Biodeg
Heptanoic acid, ester with 2,2,4 -trimethyl-1,3-pentanediol *	√	√	√	√	TD	TD	R	R	R	√
Stearic acid, 2-hydroxyethyl ester	√	R	R	R	TD	TD	R	R	R	R
Triethylene glycol, diheptanoate *	R	R	√	R	TD	TD	√	√	√	√
Propylene glycol, monostearate *	√	√	√	R	TD	TD	R	R	R	R
Heptanoic acid, oxybis(2,1-ethanediyloxy-2,1-ethanediyl) ester	√	√	√	√	TD	TD	√	√	√	√
9-Octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol	√	R	R	R	TD	TD	R	√	R	√
Decanoic acid, mixed diesters with octanoic acid and triethylene glycol	R	R	R	R	TD	TD	R	R	R	R
Hexanoic acid, 2-ethyl-, diester with tetraethylene glycol	R	R	R	R	TD	TD	R	R	R	R
Propylene glycol dilaurate*	√	R	R	R	TD	TD	R	R	R	R
Stearic acid, ethylene ester	√	R	R	R	TD	TD	R	R	R	R
Oleic acid, propylene ester	R	R	R	R	TD	TD	R	R	R	R
Propylene glycol diisostearate*	√	R	R	R	TD	TD	R	R	R	R
9-Octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediyl ester	R	R	R	R	TD	TD	R	R	R	R

* Not U.S. HPV aliphatic ester; data included for read-across to other group category members
Abbreviations in table: √ = adequate data; R = read-across, TD = Technical Discussion Proposed

Group D - Aliphatic Esters comprised of Monoacids and Sorbitan - "Sorbitan Esters"

Six HPV aliphatic esters were organized under Group D. These substances have the distinguishing feature that sorbitan consititutes the alcohol portion of the ester. Sorbitan is derived from the carbohydrate sugar, sorbitol, and has four hydroxy groups available for esterification. The acid portion of the sorbitan esters is comprised mainly of fatty acids such as lauric, stearic and oleic acids. Four of the HPV glycol esters were sorbitan monoesters and two substances had multiple ester linkages (i.e., sorbitan sesquioleate and sorbitan trioleate). One non-HPV sorbitan ester, sorbitan, fatty acid C6-10 tetraester (CAS 228573-47-5), was also reviewed because it provided useful data for bridging the toxicity of substances in this group and it represented a tetraester derivative of sorbitan.

Physicochemical Properties

The measured and calculated physicochemical properties for the HPV and non-HPV sorbitan esters are summarized in Table 2D. EPIWIN was used to compute these properties for comparison with experimental values and for use in predicting the environmental distribution of the substances in this group (EQC model). Hydrolysis half-lives and atmospheric photodegradation rates were computed using EPIWIN.

The HPV sorbitan esters covered the C18-C60 carbon number range. The fatty acids ranged from C10 (lauric) to C18 (stearic and oleic) acids in these materials. The chain-length of the fatty acid in the sorbitan monoesters influenced water solubility, boiling point and lipophilicity. The degree of esterification (monooleate *versus* trioleate) will also influence these properties. Hence, the water solubility of sorbitan monolaurate (C12 acid) (CAS 1338-39-2) is predicted to be much greater than that of sorbitan monostearate or sorbitan monooleate (C18 acids). The monooleate was predicted to have greater solubility in water than the corresponding sesquioleate or trioleate ester of sorbitan.

No further measurements in physicochemical properties are necessary for substances in this group.

Mammalian Toxicity

Acute Toxicity. Acute toxicity data reported for five of the six HPV sorbitan esters indicate that they have a low order of toxicity (Table 3D). The oral LD50 in rats ranged from >15.9 g/kg to > 39.8 g/kg. In addition, sorbitan, fatty acid C6-10 tetraester (CAS 228573-47-5), a non-HPV substance, has been tested in rats and its oral LD50 value was determined to be >2 g/kg. Numerous other sorbitan esters have been studied by acute oral and dermal administration. Results from these studies support the general conclusion that sorbitan fatty acid esters have low orders of acute toxicity (Elder, 1985a; CIR, 1999). Hence, no further testing for acute toxicity is necessary.

Repeated Dose Toxicity. A large number of subchronic oral and dermal studies and chronic oral feeding studies have been carried out for sorbitan monolaurate, sorbitan monostearate and sorbitan monooleate (CIR, 1999). It is beyond the scope of this paper to discuss all the subchronic and chronic toxicity studies for these three sorbitan monoesters. The comprehensive review papers by Elder (1985a) and Andersen (CIR, 1999) should be consulted for more information on the numerous repeated dose toxicity studies carried out to date for these as well as various other sorbitan esters. A few repeated dose oral feeding studies have been highlighted in Table 3D and are briefly described below.

For sorbitan monostearate, no adverse effects were reported in rats fed 5% concentrations of the test substance in the diet for 6 weeks. The NOAEL was estimated to be 5% or approximately 2500 mg/kg/day (Hendy et al. 1978). In 16-week oral studies with sorbitan monooleate, rats were fed 0, 2.5, 5 and 10% concentrations of the test substance in the diet (Ingram et al. 1978). The LOAEL was 2.5% dietary concentration (~1800 mg/kg/day) based on increased kidney weight findings that were considered significant in both male and female rats. In 13-week feeding studies with sorbitan monolaurate in rats, the LOAEL was 2.5% or approximately 2200 mg/kg/day (Cater et al. 1978).

In 2-year feeding studies at 5, 10 and 20% in the diet, Oser et al. (1957) have reported that rats tolerated sorbitan moonostearate with no adverse effects. However, at 20%, there was a small but significant decrease on growth rate in male rates. Hence, the NOAEL was 10% in the diet or approximately 5000 mg/kg/day in rats, based on these findings. In a 80-week dietary study in mice, no adverse effects were observed for sorbitan monostearate at 2% concentration in the diet and the NOAEL was 2% or approximately 2600 mg/kg/day (Hendy et al. 1978).

Sorbitan monooleate fed to rats at 5% concentrations in the diet for 2 years showed no adverse effects on growth, hematology, clinical chemistry, survival, organ size or histopathology (ACI, 1970). The NOAEL was 5% in the diet for sorbitan monooleate in this study.

Subchronic studies have also been carried out with sorbitan, fatty acids C6-10, tetraester (CAS 228573-47-5), a non-HPV material. Oral gavage studies for 28 days at dose levels up to 1000 mg/kg /day resulted in no systemic toxicity. Therefore, the NOAEL was 1000 mg/kg/day for this tetraester.

Hence, there is a large amount of information reported for the repeated dose toxicity of the sorbitan esters (Elder, 1985a; CIR, 1999). The available data covered the range of HPV substances in this group from sorbitan laurate to sorbitan oleate. Since the sesquioleate and trioleate of sorbitan are merely multiple ester homologs of sorbitan monooleate, they would be expected to show similar effects, given their structural similarities and potential to be metabolized to the monooleate. Thus, further repeated dose toxicity testing of substances in this group is not warranted.

Genetic Toxicity (Salmonella). Sorbitan monostearate (CAS 1338-41-6) was found to be negative in the Ames assay. In addition, the non-HPV substance, sorbitan fatty acid C6-10 tetraester (CAS 228573-47-5), did not cause any mutagenic effects in the *Salmonella in vitro* test. These substances bridge the low and high carbon range of most of the sorbitan esters and the chemistry of the sorbitan esters (i.e., sorbitan/sorbitol, natural fatty acids) does not suggest the likelihood that the sorbitan esters are electrophilic or reactive in nature. Thus, it is not likely that the substances in Group D cause mutagenic effects, and therefore, no further testing for point mutations is proposed.

Genetic Toxicity (Chromosomal Aberrations). Sorbitan monostearate did not transform primary Syrian golden hamster embryo cells. As discussed above for point mutation, the chemistry of the sorbitan esters does not suggest the likelihood that these substances, or their constituent substructures (i.e., sorbitol, fatty acids) are reactive or electrophilic in nature.

Therefore, the likelihood that the sorbitan esters may cause chromosomal mutation is very low or non-existent. Thus, no further genetic toxicity testing for chromosomal aberration is proposed for this group.

Toxicity to Reproduction. Limited reproductive toxicity data have been reported for the sorbitan esters. Oser et al. (1956) have reported that in 2-year feeding studies in rats with sorbitan monostearate, there were no effects on gestation and fertility at any dose level (0, 5, 10 and 20% in the diet) but survival of the newborn animals and maternal lactation were slightly diminished at the 20% level.

It is of interest to note that multigeneration feeding studies have been carried out by MacKensie et al. (1986) to evaluate the reproductive and developmental effects of sorbitol. Male and female rats fed up to 10% sorbitol in the diet during the 96-week study had no significant adverse clinical, behavioral, or reproductive effects, and no significant gross or microscopic changes were observed. Sorbitol was also studied indirectly as part of a mixture of hydrogenated starch hydrolysates (HSH) which contained about 7% sorbitol as part of the polyhydric alcohol mixture. The HSH mixture was investigated as part of a two-year ingestion study, a multigeneration reproduction study and a teratology study. At concentrations of 18% in drinking water (3000-7000 mg/kg/day), HSH did not produce reproductive or developmental effects (Modderman, 1993). These results indicate that sorbitol does not cause reproductive/developmental toxicity in animals. Given these findings and the low order of toxicity of natural fatty acids, it seems unlikely that sorbitan esters would present reproductive and developmental toxicity concerns. A technical discussion document is proposed to address reproductive/developmental toxicity issues based on the above considerations. Therefore, no reproductive toxicity testing is proposed.

Developmental Toxicity/Teratogenicity. No information has been reported. As discussed above, it appears unlikely that sorbitan esters pose developmental toxicity concerns and the reasoning is similar to that given for reproductive toxicity. A technical discussion document is proposed to address reproductive/developmental toxicity issues for the sorbitan esters. Therefore, no developmental toxicity testing is proposed.

Environmental Toxicity and Biodegradation

Aquatic toxicity data have been reported for the sorbitan esters. Sorbitan monolaurate and sorbitan monooleate have been tested. The non-HPV substance, sorbitan fatty acid C6-10 tetraester (CAS 228573-47-5), has also been evaluated in fish, daphnia and algae. These findings indicate that the sorbitan esters are not acutely toxic to aquatic organisms. The available data covered the range of water-soluble (e.g., monolaurate) and water-insoluble sorbitan esters (e.g., C6-C10 acid tetraester). Most of the sorbitan esters have limited water solubility and for this reason are not be likely to cause acute aquatic toxicity. In addition, metabolism of sorbitan sequioleate and sorbitan trioleate will generate sorbitan monooleate, for which aquatic toxicity data exist. Thus, there is sufficient information to "read-across" for the other sorbitan esters, based on the available data and the chemical similarities of the sorbitan esters, in general. Therefore, no further aquatic testing is necessary for Group D.

The biodegradation of sorbitan monolaurate, sorbitan monooleate and sorbitan, fatty acid C6-10 tetraester (CAS 228573-47-5), has been reported. These three sorbitan esters were biodegraded to the extent of 60-70% in 28-days, which indicate these materials undergo metabolism and degradation extensively in the aerobic environment. The sorbitan esters tested covered the range of carbon numbers (C18-C38) and included relatively water soluble (i.e., sorbitan monolaurate) as well as water-insoluble [i.e., sorbitan fatty acid C6-10 tetraester (CAS 228573-47-5)] members of the group. The high degree of biodegradation (70% in 28 days) for sorbitan tetraester (CAS 228573-47-5), in spite of its poor water solubility, indicates that enzymatic cleavage of the multiple ester linkage must be taking place in order to achieve the observed level of biodegradation. This would be consistent with the fact that fatty acids (e.g., oleic, stearic acid) arising from enzymatic ester bond cleavage of the sorbitan esters would be expected to be rapidly biodegraded (Vershueren, 1996; Swisher, 1987). In addition, enzymatic ester cleavage of sorbitan trioleate and sesquioleate would lead to sorbitan monooleate, for which biodegradation data exist. Thus, there is sufficient information to "read-across" for the other sorbitan esters, based on the available data and the similarities in chemistry and metabolism. These data are considered adequate to address the biodegradability of the HPV sorbitan ester and hence, no additional biodegradation testing is necessary. .

Overview

There are six HPV aliphatic esters in Group D. These substances have the distinguishing feature that sorbitan comprises the alcohol portion of the ester. Sorbitan is derived from the carbohydrate sugar, sorbitol, and has four hydroxy groups for possible esterification. The acid portion of the sorbitan esters is comprised mainly of natural fatty acids (e.g., lauric, stearic and oleic acids). The chemical commonality of the sorbitan substructure justifies grouping the six HPV substances together under Group D. Four of the HPV substances are sorbitan monoesters and two have multiple ester linkages (i.e., sorbitan sesquioleate and sorbitan trioleate). The sorbitan esters on the HPV list covered the C18-C60 carbon number range and contained fatty acids in the C6-C18 carbon number range. Three of the substances (i.e., oleate esters of sorbitan) are essentially the same, exception for the degree of esterification.

Sorbitan esters are non-ionic surfactant-active agents that typically find use as emulsifiers, stabilizers, and thickeners in foods, cosmetics, medical products, lubrication and other applications. Many of the HPV sorbitan esters have widespread use in cosmetic and pharmaceutical applications. More importantly, there exist an extensive database of toxicity and health safety information for many of these sorbitan esters (Elder, 1985a; CIR, 1999). Based on the chemical similarity among the HPV sorbitan esters and the toxicity data available for sorbitan stearate, oleate and laurate, and other tested substances, there are sufficient data to cover the majority of the carbon numbers in this group. The chemical structural similarities between HPV sorbitan esters permit "read-across" assessments and support the scientific justification for bridging data gaps for toxicity endpoints for the less-studied members of this group.

Physicochemical properties and environmental fate information are provided in Table 2D. A summary of the available toxicology data is shown in Table 3D. No additional testing is proposed for Group D.

Group D	Acute	Repeat dose	Genetic tox (mutation)	Genetic tox (chrom ab)	Reprod	Develop	Acute fish	Acute daphnia	Algal	Biodeg
Sorbitan monolaurate	√	√	R	R	TD	TD	√	R	R	√
Fatty acids, coco, monoesters with sorbitan	R	R	R	R	TD	TD	R	R	R	R
Sorbitan monostearate	√	√	√	√	TD	TD	R	R	R	R
Sorbitan monoleate	√	√	R	R	TD	TD	√	R	R	√
Sorbitan sesquioleate	√	R	R	R	TD	TD	R	R	R	R
Sorbitan, fatty acids C6-10 tetraester *	√	√	√	R	TD	TD	√	√	√	√
Sorbitan trioleate	√	R	R	R	TD	TD	R	R	R	R

* Not U.S. HPV aliphatic ester; data included for read-across to other group category members
Abbreviations in table: √ = adequate data; R = read-across, TD = Technical Discussion Proposed

Group E - Aliphatic Esters, comprised of Monoacids and Trihydroxy or Polyhydrol Alcohols - "Polyol Esters"

Fifteen HPV aliphatic esters were organized into Group E. These substances are structurally related "polyol esters" derived from common fatty acids, ranging from C5-C18 in carbon number and often containing natural fatty acids (e.g., oleic, stearic acid). The distinguishing "polyol" portion of the ester molecule consists of either:

- Pentaerythritol (PE),
- Trimethylolpropane (TMP) or 2-ethyl-2-(hydroxymethyl)-1,3-propanediol, or
- Dipentaerythritol (diPE).

Since multiple hydroxy groups are present in these polyols (see Section 2.3 for structures), Group E esters may have multiple ester linkages and may include mixed esters having different carbon-length fatty acids. Seven other polyol esters, which are not on the HPV list, were also reviewed because they were chemically similar and provided useful data for bridging the toxicity of substances in this group.

These seven non-HPV polyol esters are:

- TMP ester of heptanoic and octanoic acid,
- Heptanoic acid ester with TMP (CAS 71839-38-8),
- Hexanedioic acid, mixed esters with C9-C11 alcohols and TMP (CAS 180788-27-6),
- Hexanedioic acid, mixed esters with heptanoic, octanoic and decanoic acid and PE (CAS 68130-55-2),
- Fatty acids, C5-C9, esters with PE,
- Fatty acids, C6-C10, tetraester with PE, and
- Fatty acids, C5-C9, esters with dipentaerythritol

Physicochemical Properties

The physicochemical properties for the fifteen esters were either determined experimentally or were calculated using EPIWIN and are summarized in Table 2E. Computer models were also used to estimate these properties for comparison with measured values and to help predict the environmental distribution of the HPV Group E polyol esters.

In general, the polyol esters have molecular weights of greater than 400, have high boiling points greater than >400°C and are expected to be relatively non-volatile, lipophilic (log $P > 7$) and are relatively water-insoluble.

Hydrolysis half-lives, atmospheric photodegradation rates, and distribution between the environmental compartments for Group E polyol esters were calculated using EPIWIN and are summarized in the Table 2E.

Sufficient physicochemical data exist for the Group E polyol esters and no additional testing is needed.

Mammalian Toxicity

Acute Toxicity. Twelve (12) of the 22 polyol esters in Group E have been adequately tested for acute oral toxicity. The acute oral LD50 for these substances was greater than 2000 mg/kg indicating a relatively low order of toxicity. The similarity in the low order of toxicity for these substances is consistent with their similar chemical structure and physicochemical properties and supports the scientific justification for bridging data gaps. Consequently, no additional acute toxicity testing is proposed.

Repeated Dose Toxicity. The HPV Challenge Program requires that a repeated-dose toxicity study be performed or bridged to structurally related analog compounds. Only limited repeated-dose toxicity data are available for the HPV substances listed in Group E. However, adequate data for repeated-dose toxicity are available for six structurally related non-HPV polyol esters, and no additional testing is proposed.

The HPV substance, TMP ester (C8, C10 acid) (CAS 11138-60-6), was evaluated for repeated dose toxicity in a 28-day dermal study. The effects noted as a result of treatment (viz., decrease in body weight and serum protein values) were slight and of little toxicological concern. There was no evidence of microscopic changes noted in the histopathological evaluation; therefore, the NOAEL for TMP ester (C8, C10 acid) was 2000 mg/kg/day.

Five 28-day oral toxicity studies in rats and one 28-day dermal toxicity study in rats, exist for the following structurally related non-HPV polyol esters [designated **(a)** to **(e)** for discussion in text]:

Repeated-dose Oral Toxicity

(a) TMP esters of heptanoic and octanoic acid
(b) Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol
(c) Hexanedioic acid, mixed esters with C10-rich, C9-11 isoalcohols and TMP
(d) Fatty acid, C6-10, tetraesters with PE
(e) Fatty acid, C6-10, tetraesters with PE

Repeated-dose Dermal Toxicity

(f) Hexanedioic acid mixed esters with decanoic acid, heptanoic acid, octanoic acid and PE

Repeated-dose Oral Toxicity

The non-HPV structurally related polyol esters, **(a)** through **(e)**, were well tolerated by rats in the 28-day oral toxicity studies. The NOAEL for these substances was 1000 mg/kg/day in Sprague-Dawley rats. The non-HPV polyol ester **(a)** (which is TMP ester of heptanoic and octanoic acid), was also well tolerated by rats in a 28-day oral toxicity study. This material did not produce signs of overt systemic toxicity at any dose levels tested (i.e., 100, 300, and 1000 mg/kg/day). There were no treatment-related clinical in-life, functional observation battery, or gross postmortem findings. There were no treatment related mortality, and no adverse effects on body weight, food consumption, clinical laboratory parameters, or organ weights. However, there were increased numbers of hyaline droplets in the proximal cortical tubular epithelium of the 300 and 1000 mg/kg/day in male rats. Based on these findings (hyaline droplets), the NOAEL for the polyol ester **(a)** (i.e., TMP esters of heptanoic and octanoic acid) was established at 100 mg/kg/day for male rats. Hyaline droplet formation observed in the male kidneys is believed to be a sex/species condition specific to only male rats, which has little relevance to humans.

Repeated-dose Dermal Toxicity

The polyol ester **(f)** (which is hexanedioic acid, mixed esters with decanoic acid, heptanoic acid, octanoic acid and PE) was applied to the skin of groups of 10 (male and female) rats for five days a week for four (4) weeks at dose levels of 0, 125, 500 and 2000 mg/kg/day. Treated animals exhibited no signs indicative of systemic toxicity. No visible signs of irritation were observed at treatment sites. Microscopically, treated skin (viz., greater than or equal to 500 mg/kg/day) exhibited a dose-related increased incidence and severity of hyperplasia and hyperkeratosis of the epidermis and sebaceous gland hyperplasia. These effects were reversible. None of the minor changes in hematology and serum chemistry parameters were considered biologically significant. High dose females (2000 mg/kg/day) exhibited a significant increase in relative adrenal and brain weights when compared to the controls. These differences were attributed to the lower final body weight of the female animals. The NOAEL in this study for systemic toxicity was established as 500 mg /kg/day and 125 mg/kg/day for skin irritation.

Seven repeated-dose toxicity studies using two different routes of administration have been conducted with one HPV listed substance, decanoic acid, ester with 2-ethyl-2-(hydroxy methyl)-1,3-propanediol octanoate (CAS 11138-60-6), and six non-HPV structurally related polyol esters (see Table 3E). The results from these repeated dose toxicity studies suggest that polyol esters exhibit a low order of toxicity following repeated application. This may be attributable to similarities in their chemical structures, physicochemical properties, and common metabolic pathways (i.e., esters can be enzymatically hydrolyzed to the corrresponding polyalcohol and the corresponding fatty acids) which would support scientific justification for using the matrix set of toxicity information for bridging data gaps within Group E. Hence, by bridging these data, the polyol esters have been evaluated adequately for repeated exposure toxicity, and no additional testing is proposed for Group E.

Genetic Toxicity (Salmonella). The majority of the HPV and non-HPV substances in Group E (11 of 22 substances) have been adequately tested for genetic activity in the Salmonella assay, and all were inactive. This suggests that all the polyol esters and structural analogs lack genetic activity due to their similarity in chemical structure and physicochemical properties and support scientific justification for bridging data gaps. Consequently, no additional point mutation assays in bacterial cells or mammalian cells are proposed for substances in this group.

Chromosomal Aberrations. Seven (7) representative members of the polyol esters group have been adequately tested for chromosomal mutation in the *in vitro* mammalian chromosome aberration assay, and all were inactive. Two TMP esters were also tested for *in vivo* chromosomal aberration in rats, and both demonstrated no activity. Thus, it is unlikely that these substances are chromosomal mutagens. No further genotoxicity testing for chromosomal aberrations is proposed for the Group E polyol esters.

Toxicity to reproduction. The HPV listed substance, decanoic acid, ester with 2-ethyl-2-(hydroxy methyl)-1,3-propanediol octanoate (CAS 11138-60-6) (which is a TMP ester with C8, C10 acid) was evaluated for reproductive/developmental toxicity. According to the sponsor of the study, the test material showed no reproductive/developmental effects. Negotiations are underway in order to obtain a copy of the final report. No other reproductive toxicity studies have been conducted with polyol esters; however, no adverse effects to reproductive tissues were observed in the repeated dose toxicity studies. Since metabolism of the polyol esters can occur, leading to the generation of the corresponding fatty acids and the polyol alcohol (such as pentaerthyritol, trimethylolpropane, and dipentaerythritol), the issue of whether these metabolites may pose any potential reproductive/developmental toxicity concerns is important to address. However, the polyol alcohols such as pentaerthyritol, trimethylolpropane, and dipentaerythritol, would be expected to undergo further metabolism, conjugation and excretion in the urine. Available evidence indicates that these ester hydrolysates (i.e., hydrolysis products), primarily fatty acids (e.g., heptanoic, octanoic, and decanoic acids; see Cragg, 2001a) and secondarily the polyol alcohols should exhibit a low order of reproductive toxicity. A technical discussion document is proposed to address any potential reproductive toxicity concerns of polyol esters. Thus, it can be concluded that this group of high molecular weight polyol esters should not produce profound reproductive effects in rodents and no further testing of substances is warranted.

Developmental Toxicity. The HPV listed substance, decanoic acid, ester with 2-ethyl-2-(hydroxy methyl)-1,3-propanediol octanoate (CAS 11138-60-6) (which is a TMP ester with C8, C10 acid) was evaluated for reproductive/developmental toxicity. According to the sponsor of the study, the test material showed no reproductive/developmental effects. Negotiations are underway in order to obtain a copy of the final report. No other developmental toxicity studies have been conducted with polyol esters. Since metabolism of the polyol esters can occur, leading to the generation of the corresponding fatty acids and the polyol alcohol (such as pentaerthyritol, trimethylolpropane, and dipentaerythritol), the issue of whether these metabolites may pose any potential reproductive/developmental toxicity concerns is important to address. However, the polyol alcohols such as pentaerthyritol, trimethylolpropane, and dipentaerythritol, would be expected to undergo further metabolism, conjugation and excretion in the urine. Available evidence indicates that these ester hydrolysates, primarily fatty acids (e.g., heptanoic, octanoic, and decanoic acids; see Cragg, 2001a) and secondarily the polyol alcohols should exhibit a low order of reproductive/developmental toxicity. A technical discussion is proposed to address any potential developmental toxicity concerns of polyol esters. Thus, it can be concluded that this group of high molecular weight polyol esters should not cause fetal toxicity and developmental anomalies in rodents and no further testing of substances is warranted.

Environmental Toxicity and Biodegradation

Acute aquatic toxicity studies have been carried out for most of the HPV polyol esters and the non-HPV polyol esters. There is sufficient information on the aquatic toxicity of many of the Group E polyol esters in fish, invertebrates and algae (Table 3E). In general, the tested polyol esters do not cause acute toxicity to aquatic organisms. In addition, polyol esters have very limited water solubility and these materials are probably not likely to cause toxicity at their maximum water solubility. The matrix set of available aquatic toxicity data provides adequate information for read-across assessment and for bridging the toxicity data gaps for polyol esters. For these reasons, no additional aquatic toxicity testing is necessary for substances in this group.

Biodegradability results have been reported for seven of the 15 HPV polyol esters as well as four of the seven non-HPV polyol esters (see Table 3E). All of the tested polyol esters showed extensive biodegradation in the standard 28-day test and these findings indicate that polyol esters are capable of undergoing metabolic ester cleavage, which leads to the generation of the corresponding fatty acids as well as the polyol alcohols.

Interestingly, the "readily" biodegradability findings observed for some polyol esters (especially pentaerythritol esters and those with natural fatty acids such as oleic acid) indicate that enzymatic cleavage of the ester linkage(s) must be occurring significantly, in order to achieve the high level of biodegradation observed. This would be consistent with the fact that fatty acids (e.g., oleic acids), arising from enzymatic cleavage of the polyol esters, are rapidly biodegraded (Vershueren, 1996; Swisher, 1987). In addition, the results are also consistent with the fact the pentaerythritol itself is readily biodegradable (84% biodegradation in 28 days) (Birch et al. 1991). Thus, there is sufficient biodegradability information available from the matrix set of HPV and non-HPV substances to provide useful data for "read-across" for other polyol esters in Group E, based on chemical similarities, type of polyol ester and fatty acids. For these reasons, the dataset available for the polyol esters is considered adequate to address the biodegradability of the HPV polyol esters, and hence, no additional biodegradation tests are proposed for substances in Group E.

Overview

As discussed earlier, fifteen HPV polyol esters were organized into Group E. These substances were grouped together since they represented structurally related "polyol esters" which are comprised of fatty acids that are linked to one of the multiple hydroxyl groups of the polyol. The polyol molecule can be pentaerythritol (PE), trimethylolpropane (TMP) or dipentaerythritol (diPE). The fatty acids can range from C5-C18 in carbon number and often contain the natural fatty acids, oleic and stearic acids. The fifteen HPV polyol esters fall in the C24-C77 carbon range; for this reason, most of the polyol esters have high boiling points, low volatility, low water-solubility and high lipophilic characteristics.

Seven other non-HPV polyol esters, especially TMP esters of heptanoic and octanoic acid; heptanoic acid ester with TMP (CAS 71839-38-8); hexanedioic acid, mixed esters with C9-C11 alcohols and TMP (CAS 180788-27-6); hexanedioic acid, mixed esters with heptanoic, octanoic and decanoic acid and PE (CAS 68130-55-2); and fatty acids, C6-C10, tetraester with PE, have been extensively tested (Table 3E). They are included in this review mainly because they provide useful toxicological data for assessing the Group E substances.

The chemical structure similarities among the polyol esters support scientific justification for bridging data gaps within this group. The physicochemical, environmental and toxicological data from the HPV and the non-HPV materials cover the majority of carbon numbers in the polyol esters within this group.

Physicochemical properties and environmental fate information are provided in Table 2E. A summary of the available toxicology data is shown in Table 3E. No additional testing is proposed for Group E.

Group E Name (Type Ester; Acids)	Acute	Repeat dose	Genetic tox (mutation.)	Genetic tox (chrom aber.)	Reprod	Develop	Acute fish	Acute daphnia	Algal	Biodeg
Decanoic acid, mixed esters with heptanoic acid, octanoic acid and trimethylolpropane (TMP Ester; C7, 8, 10 Acid)	R	R	R	R	TD	TD	R	R	R	R
Trimethylolpropane esters of heptanoic and octanoic acid (TMP Ester; C7,8 acid) *	√	√	√	√	TD	TD	√	√	√	√
Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (TMP Ester; C7 acid)*	√	√	√	√	TD	TD	√	R	R	√
Hexanedioic acid, mixed esters with C10-rich, C9-11 isoalcohols and TMP (TMP+C10+iso-C9-11 Alcohols, Mixed Ester, with C6-dioic acid)*	√	√	√	√	TD	TD	√	√	√	√
Decanoic acid, ester with 2-ethyl-2-(hydroxy-methyl)-1,3-propanediol octanoate (TMP Ester; C8, C10 acids)	√	√	√	√	√	√	√	√	√	√
Nonanoic acid, triester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (TMP Triester; C9 acid)	√	R	R	√	TD	TD	√	√	√	√
Fatty acids, C14-18 and C16-18 unsatd, triesters with trimethylolpropane (TMP Triester; C14-18 satd,C16-18 unsatd acid)	R	R	R	R	TD	TD	R	R	R	R
9-Octadecenoic acid (Z)-, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (TMP monoester; oleic C18 acid)	√	R	R	R	TD	TD	√	R	R	√
9-Octadecenoic acid (Z)-,2-ethyl-2-[(1-oxo-9-octadecenyl)oxy]methyl]-1,3-propanediyl esterZ (TMP diester; oleic C18 acid)	R	R	R	R	TD	TD	R	R	R	√
Carboxylic acids, C5-9, tetraesters with pentaerythritol (PE tetra ester; C5-9 acids)	√	R	√	R	TD	TD	√	R	R	√
Decanoic acid, mixed esters with heptanoic acid, isovaleric acid, octanoic acid and pentaerythritol (PE mixed esters; C7-8, 10 acids)	R	R	R	R	TD	TD	R	R	R	R
Fatty acids, C5-10, esters with pentaerythritol (PE esters, C5-10 acids)	R	R	R	R	TD	TD	R	R	√	R
Hexanedioic acid mixed esters with decanoic acid, heptanoic acid, octanoic acid and PE (PE Mixed Ester; C6,7,8,10 acids)*	√	√	√	√	TD	TD	√	√	√	√
Nonanoic acid, neopentanetetrayl ester (PE Tetraester; C9 acids)	R	R	R	R	TD	TD	R	R	R	R
Pentaerythritrol, tetrastearate (PE Tetraester; C18 acids	R	R	R	R	TD	TD	R	R	R	R
Fatty acids, C5-9, esters with pentaerythritol (PE Esters; C5-9 acids)*	√	R	√	R	TD	TD	R	R	R	R
Fatty acid, C6-10, tetraesters with PE (PE Tetraester; C9-10 acids)*	√	√	√	√	TD	TD	√	√	√	√
Linseed oil, ester with pentaerythritol (PE ester; oleic, linoleic, linolenic C18 acids)	√	R	R	R	TD	TD	R	R	R	R
Fatty acids, tall oil, tetra esters with pentaerythritol (PE tetraester; oleic, linoleic, C18 acids)	R	R	R	R	TD	TD	R	R	R	R
Fatty acids, C5-10, esters with dipentaerythritol DiPE hexaester; C5-10 acids	√	R	R	R	TD	TD	R	R	√	R
Fatty acids, C5-10, esters with dipentaerythritol DiPE hexaester; C5-9 acids	√	R	√	R	TD	TD	√	R	R	√
Fatty acids, C5-9, esters with dipentaerythritol (diPE Ester; C5-9 acids)*	√	R	√	R	TD	TD	R	R	R	R

*Not U.S. HPV aliphatic ester; data included for read-across to other category members.

√ = adequate data; R = read-across; R = read-across; TD = Technical Discussion proposed

5.0 TEST PLAN SUMMARY

The American Chemistry Council's Aliphatic Esters Panel believes that sufficient health effects and toxicity data exist for the aliphatic esters (and for structurally related and analogous chemicals) to substantially characterize the human health effects, aquatic toxicity and biodegradation endpoints for all the members of this chemical category under the HPV program. No additional toxicity tests are proposed for the aliphatic esters as a chemical category.

The following technical discussions will be developed to complete the health hazard assessments for genetic toxicity (chromosomal aberrations) and for reproductive and/or developmental toxicity endpoints of select groups as noted in Section 4. These include:

- Prepare a technical discussion to explain why Group A monoesters are not likely to cause chromosomal aberration based on their non-reactive and non-electrophilic character and their inherent chemistry.
- Prepare a technical discussion to highlight why glycol esters are not expected to be metabolized in the same manner as polyethylene glycol ethers to methoxyethanol or ethoxyethanol and as a result, account for why the glycol esters in Group C are not likely to cause reproductive/developmental toxicity concerns in the same way as the polyethylene glycol ethers.
- Prepare a technical discussion to explain why the Group D sorbitan esters are not likely to cause reproductive and developmental toxicity in rodents based on the findings that sorbitan monostearate does not cause effects on fertility or gestation in 2-year feeding studies, and based on the multigeneration feeding and teratology studies that showed no reproductive or developmental toxicity for sorbitol.
- Prepare a technical discussion to address the reproductive/developmental toxicity potential of Group E polyol esters and its constituent free polyols and free fatty acids, that may arise from metabolism. Unpublished data indicate that polyol esters such as the TMP mixed ester of octanoic and decanoic acid (CAS 11138-60-6) do not cause reproductive or developmental toxicity in rodents. The discussion will address these findings as well as the low order of toxicity associated with the free polyols and constituent free fatty acids.

For the physicochemical properties and fugacity transport endpoints, the following modeling technical discussion will be developed:

- Calculate physicochemical data and fugacity transport data for the seven non-HPV reference chemicals in Group E, which were used as reference compounds in the matrix data analysis and in read-across assessments to bridge toxicity data gaps in this group. Appropriate QSAR models (e.g., EPIWIN and EQC) will be used to calculate these values which will be supplemented with measured data, if available.

Robust summaries of existing health effects, environmental fate and effects, and physicochemical properties data are attached in the Appendices. In summary, the extensive data available and the test plan described in Section 4, along with the technical discussions, will provide adequate information to substantially and adequately characterize the human health effects, physicochemical properties and environmental fate and effects endpoints for the aliphatic esters under the HPV Chemical Challenge Program.

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* The list of references is not a comprehensive bibliography of all the aliphatic ester literature. Pertinent papers cited in the text are those that are important in health hazard assessments or in bridging toxicity gaps for structurally similar esters in the various group subcategories. The information and data in the papers and reviews supplement the robust summaries developed for the toxicology studies of the HPV substances, which are ultimately used to address the SIDS toxicity endpoints for the HPV aliphatic esters.

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7.0 List of Tables and Figures

Table 2A. Group A - Aliphatic Esters, comprised of Monoacids and Monoalcohols
Summary Table of Physicochemical Data for "Monoesters"

Total Carbon Number in Ester	MW	CAS Number	Chemical Name	MP* (°C)	BP** (°C)	Vapor Pressure (Pa@25°C)	Octanol-Water Partition Coefficient (log Pow)	Water Solubility (mg/L @25°C)	Photo-degradation Half-life (days)	Hydrolysis Half-life (yrs)	Transport (%) c			
											Soil	Air	Water	Sediment
22	341	123-95-5	Stearic acid, butyl ester	26-27 109 c	343 384 c	1.27 E-05 (20) 8.1 E-04 c	9.7 c	3.6 E-05 c	0.411 c	9.09 c	27.8	0.07	7.25	64.3
24	369	29806-73-3	Palmitic acid, 2-ethylhexyl ester	117 c	400 c	1.02 E-06 c	10.6 c	4.13 E-06 c	0.36 c	14.1 c	28.3	0.57	7.2	63.9
26	393-395	68334-13-4	Fatty acids, tall oil, 2-ethylhexyl ester	114 c	427 c	1.98 E-05 c	11.4 c	6.3 E-07 c	0.056 c	0.056 l/mol s c	28	0.5-0.9	7.3	64-69
26	397	85049-37-2	Fatty Acids, C16-18 satd and C18 unsatd, 2-ethylhexyl ester	135 c	423 c	1.76 E-07 c	11.6 c	4.02 E-07 c	0.331 c	14.1 c	29.1	0.1	7.1	63.3
26	397	109-36-4	Stearic acid, octyl ester	145 c	430 c	9.28 E-08c	11.67 c	3.48 E-07c	0.34 c	20.4 c	29.5	0.48	7.09	62.9
28	423	3687-46-5	Oleic acid, decyl ester	161 c	457 c	1.31 E-08c	12.44 c	5.3 E-08 c	0.12 c	20.4 c	28.5	0.09	7.23	64.2
31	467	31556-45-3	Stearic acid, tridecyl ester	190 c	488 c	1.40 E-07 c	14.1 c	1.0 E-09 c	0.28 c	20.4 c	30.9	0.35	7.0	61.8
32	481	17661-50-6	Stearic acid, myristyl ester	54 192 c	500 c	1.5 E-08 c	14.6 c	3.13 E-10 c	0.27 c	20.4 c	29.8	0.38	7.07	62.8
34	494	25339-09-7	Stearic acid, isocetyl ester	207 c	516 c	1.25 E-10 c	15.52 c	3.47 E-11 c	0.25 c	20.4 c	30	0.13	3.4	66.6

Highlighted rows are not on the HPV list but included to facilitate category evaluation

c = calculated data using EPWIN; all other values are derived from measurements
* = Note: Mixtures are expected to have melting points below those of pure components. Modeled data do not accurately reflect melting points for these substances.
** = boiling points for some esters may have been determined under reduced pressure.

Table 2B. Group B - Aliphatic Esters, comprised of Diacids and Monoalcohols
Summary Table of Physicochemical Data for "Diesters" (e.g., Adipates, Maleates, Azelates, Sebacates)

Total Carbon Number in Ester	MW	CAS Number	Chemical Name	MP* (°C)	BP** (°C)	Vapor Pressure (Pa@25°C)	Octanol-Water Partition Coefficient (log Pow)	Water Solubility (mg/L @25°C)	Photo-degradation Half-life (days)	Hydrolysis Half-life (yrs)	Transport (%) c			
											Soil	Air	Water	Sediment
12	228	105-76-0	Maleic acid, dibutylester	< -60 -28 c	277-288 267 c	<1 E-02 hPa 5.32 E-03 c	3.38 4.16 c	173 (20 C) 8.7 c	0.33 c	0.33 0.33 c	55.9	2.7	39.3	2.2
16	284	105-52-2	Maleic acid, bis(1,3-dimethylbutyl)ester	-28 c	292 c	0.0297 c	5.8 c	0.16 c	0.23 c	12.2 c	37.3	0.9	16.4	45.3
20	341	142-16-5	Maleic acid, bis(2-ethylhexyl)ester	-60 pour pt 29 c	164 (10mmHg) 360 c	7.2 E-05 c	7.9 c	0.00117 c	0.19 c	0.52 c	29.6	1.1	11.2	58.1
12	230	6938-94-9	Adipic acid, diisopropyl ester	-1 -48 c	120 (6.5 mmHg) 136 (14 mm Hg) 241 c	0.0446 c	3.2 c	55.6 c	1.03 c	2.33 c	58.8	2.7	38	0.6
14	258	105-99-7	Adipic acid, dibutyl ester	-11 -6.6 c	294 c	0.00273 c	4.33 c	4.2 c	0.84 c	2.07 c	54	3.6	39.3	3.1
21	356	68515-75-3	Adipic acid, di-C7-9 branched and linear alkyl esters	< 0 30 c	361 c	8.89 E-03 c	7.55 c	0.0020 c	0.45 c	3.21 c	27.3	0.3	3.6	68.8
22	370	1330-86-5	Adipic acid, diisooctyl ester	-70 9 c	>300 379 c	3.53 E-03 c	8.12 c	5.45 E-04 c	0.45 c	2.07 c	27.3	0.3	3.5	69
22	370	108-63-4	Adipic acid, bis(1-methylheptyl) ester	9 c	175 (2 mmHg) 379 c	2.65 E-05 c	8.1 c	0.00545 c	0.42 c	2.33 c	29.5	1.2	11.1	58.2
22	370	103-23-1	Adipic acid, bis(2-ethylhexyl) ester	-79 9 c	417 379 c	6.3 E-05 3.5 E-05 c	8.12 c	3.2 E-03 (1) 5.45 E-04 c	0.40 c	3.2 c	31.4	1.0	10.8	56.8
22	435	141-17-3	Adipic acid, bis[2-(2-butoxyethoxy)ethyl]ester	117 c	441 c	9.84 E-08 c	3.2 c	3.2 c	0.15 c	0.81 c	71.7	0	27.8	0.4
24	399	33703-08-1	Adipic acid, diisononyl ester	< -60 56 c	> 300 416 c	0.9 (200 mgHg) 2.25 E-04 c	9.24 c	2.2 E-04 (1) 3.98 E-05 c	0.40 c	4.64 c	28.8	0.6	7.2	63.4
26	427	27178-16-1	Adipic acid, diisodecyl ester	< -60 51 c	> 300 426 c	1.69 E-06 1.51 E-04 c	10.1 c	4.4 E-05 (1) 5.15 E-06 c	0.36 c	2.07 c	28.5	0,2	3.4	67.9
32	511	16958-92-2	Adipic acid, ditridecyl ester	< 0 141 c	509 c	1.45 E-07 c	13.17 c	3.43 E-09 c	0.28 c	4.64 c	31.0	0.4	7.0	61.7
25	413	103-24-2	Azelaic acid, bis(2-ethylhexyl)ester	-78 41 c	237 (5 mmHg) 414 c	1.66 E-05 c	9.6 c	1.65 E-05 c	0.36 c	3.22 c	28.4	0.6	7.2	63.8
29	469	28472-97-1	Azelaic acid, diisodecyl ester	83 c	460 c	7.61 E-08 c	11.6 c	1.54 E-07 c	0.32 c	2.1 c	29.8	0.2	3.4	66.6
12	230	106-79-6	Sebacic acid, dimethyl ester	38 -27 c	261 c	0.011 c	3.4 c	120 41.7 c	1.1 c	3.6 c	60.1	2.5	36.7	0.7
26	469	122-62-3	Sebacic acid, bis(2-ethylhexyl)ester	51 c	212 (1mm Hg) 426 c	1.97 E-06 c	3.74 10.1 c	1.5 E-07 c	0.35 c	7.1 c	28.7	0.5	7.2	63.6

Highlighted rows are not on the HPV list but included to facilitate group category evaluation

c = calculated data using EPWIN; all other values are derived from measurements

* = Note: Mixtures are expected to have melting points below those of pure components. Modeled data do not accurately reflect melting points for these substances.

** = many of the esters have boiling points determined under reduced pressure and some values have been extrapolated to one atmosphere

(1) Recent water solubility data were determined by the method of D Letinski et al. (2001). Slow-stir water solubility measurements of selected alcohols and diesters (manuscript submitted to Chemosphere)

Table 2C. Group C - Aliphatic Esters, comprised of Monoacids and Dihydroxy Alcohols
Summary Table of Physicochemical Data for "Glycol Esters"

Total Carbon Number in Ester	MW	CAS Number	Chemical Name	MP* (°C)	BP** (°C)	Vapor Pressure (Pa@25°C)	Octanol-Water Partition Coefficient (log Pow)	Water Solubility (mg/L @25°C)	Photo-degradation Half-life (days)	Hydrolysis Half-life (yrs)	Transport (%) c			
											Soil	Air	Water	Sediment
15	258	71839-38-8	Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol	-50 75 c	>300 322 c	2.8 E-05 1.08 E-05 c	>6.3 4.6 c	2.7 7.84 c	0.50 c	10.6 c	58.7	1.1	32.2	7.9
20	329	111-60-4	Stearic acid, 2-hydroxyethyl ester	57-60 138 c	404c	6.58 E-08 c	7.26 c	0.01711 c	0.39 c	7.7 c	31.0	0.5	7.5	61
20	375	7434-40-4	Triethylene glycol, diheptanoate	-24 54 c	>250 (decomp) 394 c	6.29 E-06 c	4.77 c	30 0.3732 c	0.25 c	0.81 c	67.4	0.0	24.3	8.3
21	343	1323-39-3	Propylene glycol, monostearate	132 c	405 c	1.12 E-08 c	7.67 c	0.0062 c	0.34 c	7.7 c	31.3	0.4	7.1	61.2
22	419	70729-68-9	Heptanoic acid, oxybis(2,1-ethanediyloxy-2,1-ethanediyl) ester	94 c	429 c	3.39 E-07 c	2.86 4.49 c	0.3419 c	0.19 c	0.81 c	69.5	0.0	25.7	4.8
23	368	67989-24-6	9-Octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol (Monoester)	157 c	431 c	1.01 E-09 c	8.40 c	0.0010 c	0.07 c	6.5 c	28.8	0.1	7.3	63.9
24	431	68583-52-8	Decanoic acid, mixed diesters with octanoic acid and triethylene glycol	96 c	441 c	1.74 E-07 c	6.73 c	0.0035 c	0.22 c	1.1 c	42	0.0	7.3	50.7
24	447	18268-70-7	Hexanoic acid, 2-ethyl-, diester with tetraethylene glycol	89 c	439 c	2.28 E-07 c	5.33 c	0.0441 c	0.18 c	30.8 c	59.7	0.0	19.1	21.2
27	441	22788-19-8	Propylene glycol dilaurate	75 c	444 c	2.31 E-07 c	10.64 c	1.38 E-06 c	0.34 c	5.9 c	30.1	0.5	7.0	62.4
38	595	627-83-8	Stearic acid, ethylene ester (Diester)	79 212 c	189-191** 579 c	8.01 E-11 c	16.12 c	2.97 E-12 c	0.23 c	1.8 c	30.6	0.3	7.0	62.1
39	605	105-62-4	Oleic acid, propylene ester	197 c	591 c	2.0 E-12 c	16.11 c	2.61 E-12 c	0.04 c	0.73 c	27.6	0.0	3.5	68.9
39	609	68958-54-3	Propylene glycol diisostearate	175 c	569 c	1.29 E-11 c	16.39 c	1.41 E-12 c	0.22 c	5.9 c	30.4	0.1	2.3	67.2
41	633	42222-50-4	9-Octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediyl ester (Diester)	234 c	609 c	2.38 E-13 c	17.05 c	2.67 E-13 c	0.03 c	3.3 c	27.6	0.0	3.5	68.9

Highlighted rows are not on the HPV list but included to facilitate category evaluation

c = calculated data using EPWIN; all other values are derived from measurements

* = Note: Mixtures are expected to have melting points below those of pure components. Modeled data do not accurately reflect melting points for these substances.

** = boiling points for some esters may have been determined under reduced pressure.

Table 2D. Group D - Aliphatic Esters, comprised of Monoacids and Sorbitan
Summary Table of Physicochemical Data for "Sorbitan Esters"

Total Carbon Number in Ester	MW	CAS Number	Chemical Name	MP* (°C)	BP** (°C)	Vapor Pressure (Pa@25°C)	Octanol-Water Partition Coefficient (log Pow)	Water Solubility (mg/L @25°C)	Photo-degradation Half-life (days)	Hydrolysis Half-life (yrs)	Transport (%) c			
											Soil	Air	Water	Sediment
18	346	1338-39-2	Sorbitan, monolaurate	176 c	462 c	9.34 E-12 c	3.15 c	13.19 c	0.20 c	14.2 c	68.2	0.04	31.4	0.3
18-20	346-374	68154-36-9	Fatty acids, coco, monoesters with sorbitan (main fatty acids are lauric and myristic acids)	176-191 c	462-485 c	1.1-9.3 E-12 c	3.15-4.14 c	1.29-13.2 c	0.19-0.20 c	7.7 - 14.2 c	64.6-68.2	0.04-0.3	31.4-33.4	0.3-1.8
24	431	1338-41-6	Sorbitan, monostearate	222 c	531 c	1.38 E-14 c	6.10 c	0.0122 c	0.17 c	7.7 c	36.2	0.3	12.6	50.9
24	430	1338-43-8	Sorbitan, monooleate	223 c	535 c	1.03 E-14 c	5.89 c	0.0191 c	0.05 c	2.2 c	37.2	0.1	15.6	47.1
33	569	8007-43-0	Sorbitan, sesquioleate	248 c	609 c	6.83 E-17 c	10.11 c	5.93 E-07 c	0.04 c	0.90 c	28.6	0.1	7.2	64.1
38	669	228573-47-5	Sorbitan, Fatty Acid C6-10 Tetraester	< -25C 266 c	>295 C 636 c	1.7 E-07 1.87 E-14 c	>7.7 11.57 c	<0.02 7.37 E-09 c	0.19 c	0.79 c	32.1	0.5	10.7	56.7
60	958	26266-58-0	Sorbitan, trioleate	350 c	916 c	1.32 E-19 c	21.71 c	5.97 E-19 c	0.02 c	0.59 c	27.4	0.0	3.5	69.1

Highlighted rows are not on the HPV list but included to facilitate category evaluation

c = calculated data using EPWIN; all other values are derived from measurements
* = Note: Mixtures are expected to have melting points below those of pure components. Modeled data do not accurately reflect melting points for these substances.
** = boiling points for some esters may have been determined under reduced pressure.

Table 2E. Group E - Aliphatic Esters, comprised of Monoacids and Trihydroxy or Polyhydroxy Alcohols (Polyols) Summary Table of Physicochemical Data for "Polyol Esters" (e.g., TMP, PE and diPE Esters)

Total Carbon Number in Ester	MW	CAS Number	Chemical Name	MP* (°C)	BP** (°C)	Vapor Pressure (Pa@25°C)	Octanol-Water Partition Coefficient (log Pow)	Water Solubility (mg/L @25°C)	Photo-degradation Half-life (days)	Hydrolysis Half-life (yrs)	Transport (%) c			
											Soil	Air	Water	Sediment
31	513	68130-53-0	Decanoic acid, mixed esters with heptanoic acid, octanoic acid and trimethylolpropane (TMP Ester; C7, 8, 10 Acid)	148 c	505 c	1.14 E-09 c	10.68 c	4.52 E-07 c	0.31 c	0.89 c	32.9	0.7	10.5	55.8
24	415	11138-60-6	Decanoic acid, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol octanoate (TMP Ester; C8, C10 Acid)	116 c	>300 448 c	< 13 Pa 25C 8.7 E-10 c	>2.7 7.67 c	0.48 0.0023 c	0.40 c	7.3 c	34.7	0.3	6.8	58.2
33	555	126-57-8	Nonanoic acid, triester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (TMP Triester; C9 Acid)	-16 Pour pt 193 c	>300 535 c	21 Pa 25C 5.86 E-11 c	>2.8 12.11 c	8.4 1.44 E-08 c	0.32 c	7.8 c	31.3	0.4	6.9	61.4
56	875	68002-79-9	Fatty acids, C14-18 and C16-18 unsatd, triesters with trimethylolpropane (TMP Triester; C14-18 satd, C16-18 unsatd Acid)	350 c	806 c	4.4 E-20 c	23.19 c	3.6 E-20 c	0.05 c	4.2 c	27.8	0.03	3.5	68.7
24	417	70024-57-6	9-Octadecenoic acid (Z)-, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (TMP Monoester, Oleic C18 Acid)	228 c	532 c	3.82 E-14 c	6.93 c	0.00728 c	0.19 c	---	31.6	0.3	8.0	60.2
60	928	57675-44-2	9-Octadecenoic acid (Z)-, 2-ethyl-2-[(1-oxo-9-octadecenyl)oxy]methyl]-1,3-propanediyl ester, (Z)- (TMP Diester; Oleic C18 Acid)	350 c	859 c	1.47 E-21 c	24.73 c	7.8 E-22 c	0.02 c	2.2 c	27.4	0.01	3.5	69.1
33	529	67762-53-2	Carboxylic acids, C5-9, tetraesters with pentaerythritol (PE Tetraester; C5-9 Acids)	209 c	522 c	2.83 E-10 c	11.41 c	8.4 E-08 c	0.11 c	----	29.5	0.2	7.1	63.2
37	641	68130-51-8	Decanoic acid, mixed esters with heptanoic acid, isovaleric acid, octanoic acid and pentaerythritol (PE Mixed Ester; C7, 8 Acids)	242 c	601 c	3.12 E-13 c	12.56 c	1.62 -09 c	0.29 c	3.9 c	31.2	0.4	6.9	61.5
	613	68424-31-7	Fatty acids, C5-10, esters with pentaerythritol (PE Ester; C5-10 Acids)	233 c	585 c	1.4 E-10 c	11.7 c	1.5 E-08 c	---	---	34	0.7	11	55
41	697	14450-05-6	Nonanoic acid, neopentanetetrayl ester (PE Tetraester; C9 Acid)	279 c	654 c	4.13 E-15 c	14.6 c	1.25 E-11 c	0.25 c	5.8 c	30.8	0.3	7.0	61.9
77	1202	115-83-3	Pentaerythritol, tetrastearate (PE Tetraester; C18 Acid)	350 c	1072 c	1.5 E-27 c	32.3 c	3.62 E-30 c	0.12 c	5.8 c	29.4	0.04	2.4	68.2
77	1188	68648-28-2	Linseed oil, ester with pentaerythritol (PE Ester; oleic, linoleic, linolenic C18 acids)	350 c	1097 c	2.87 E-28 c	30.8 c	8.75 E-29 c	0.01 c	1.6 c	27.9	0.0	2.4	69.7
77	1190	68334-18-9	Fatty acids, tall oil, tetra esters with pentaerythritol (PE Tetraester; oleic and linoleic C18 acids)	350c	1094 c	3.63 E-28 c	31.0 c	5.55 E-29 c	0.01 c	1.6 c	27.9	0.0	2.4	69.6
60	927	70983-72-1	Fatty acids, C5-10, esters with dipentaerythritol (DiPE hexaester; C5-10 Acids)	350 c	835 c	9.3 E-19 c	15.8 c	3.6 E-14 c	---	---	34	0.4	11	55
60	955	67762-52-1	Carboxylic acids, C5-9, hexaesters with dipentaerythritol (DiPE hexaesters; C5-C9 Acids)	350 c	858 c	2.1 E-19 c	16.7 c	3.4 E-15 c	---	---	32	0.4	11	57

Highlighted rows are not on the HPV list but included to facilitate category evaluation

c = calculated data using EPWIN; all other values are derived from measurements

* = Note: Mixtures are expected to have melting points below those of pure components. Modeled data do not accurately reflect melting points for these substances.

** = boiling points for some esters may have been determined under reduced pressure.

Table 3A. Group A - Aliphatic Esters, comprised of Monoacids and Monoalcohols - "Monoesters" Summary Table of Toxicology and Biodegradation Data

Total Carbon Number in Ester	MW	CAS Number	Chemical Name	Acute Oral LD50	Repeated Dose Toxicity	Genetic Tox (Point/Gene Mutation)	Genetic Tox (Chrom. Aber.)	Toxicity to Reproduction	Developmental Toxicity/ Teratogenicity	Acute Fish LC50 or LL50	Daphnia LC50 or LL50	Algal LC50 or LL50	Biodegradation %
22	341	123-95-5	Stearic acid, butyl ester	>32 g/kg	2-Year Feeding Study (rat) 6.25% in diet showed no significant differences from control animals.			6.25% in diet for 10 weeks in rats showed no effect on fertility, litter size, survival of offspring					
24	369	29806-73-3	Palmitic acid, 2-ethylhexyl ester	>5 g/kg									
26	393-395	68334-13-4	Fatty acids, tall oil, 2-ethylhexyl ester	> 64 g/kg	Read across: (a) 28-day Oral Gavage (rat) NOAEL 1000 mg/kg								
26	397	85049-37-2	Fatty Acids, C16-18 satd and C18 unsatd, 2-ethylhexyl ester	>17.2 g/kg	Read across: (a) 28-day Oral Gavage (rat) NOAEL 1000 mg/kg	Negative (Ames)			Read-Across (b) NOAEL Teratogen > 1000 mg/kg NOAEL Maternal >1000 mg/kg	3200 mg/L	17 mg/L	40-42 mg/L	85% in 28 days OECD 301D Closed Bottle
26	397	109-36-4	Stearic acid, octyl ester	> 8 ml/kg	28-day Oral Gavage (rat) NOAEL 1000 mg/kg	Negative (Ames)			Read-Across (b) NOAEL Teratogen > 1000 mg/kg NOAEL Maternal >1000 mg/kg				
28	423	3687-46-5	Oleic acid, decyl ester	> 40 ml/kg	28-day Oral Gavage (rat) NOAEL 1000 mg/kg	Negative (Ames)				3200 mg/L	17 mg/L	40-42 mg/L	80% in 28 days OECD 301D Closed Bottle
31	467	31556-45-3	Stearic acid, tridecyl ester										
32	481	17661-50-6	Stearic acid, myristyl ester	> 10 g/kg (mice)									
34	494	25339-09-7	Stearic acid, isocetyl ester	> 10 g/kg									

Highlighted rows are not on the HPV list but included to facilitate category evaluation

Footnotes:

a) Read-across for repeated oral toxicity was based on studies with 2-ethylhexyl stearate or octyl stearate, oral gavage rat study at 100, 500 and 1000 mg/kg for 28 days. NOAEL was 1000 mg/kg.

b) Read across for developmental/teratogenicity was based on studies with 2-ethylhexyl ester of C16-18 Fatty acid (CAS 91031-48-0) (IUCLID database, 1996) since structure is very similar to octyl (=2-ethyl hexyl) stearate (CAS 109-34-4) and to Fatty Acid, C16-18 satd and C18 unsatd, 2-ethylhexyl ester (CAS 85049-37-2).

Table 3B. Group B - Aliphatic Esters, comprised of Diacids and Monoalcohols - "Diesters"
Summary Table of Toxicology and Biodegradation Data

Total Carbon Number in Ester	MW	CAS Number	Chemical Name	Acute Oral LD50	Repeated Dose Toxicity	Genetic Tox (Point/Gene Mutation)	Genetic Tox (Chrom. Aber.)	Toxicity to Reproduction	Developmental Toxicity/ Teratogenicity	Acute Fish LC50 or LL50	Daphnia LC50 or LL50	Algal LC50 or LL50	Biodegradation %
12	228	105-76-0	Maleic acid, dibutyl ester (a)	3.73 g/kg	7-Day Oral gavage study (rat) NOAEL 95 mg/kg/day based on liver and kidney effects	Negative (Ames)	Negative (micronucleus, in vivo, mouse)	Oral gavage study (rat) NOAEL 95 mg/kg/day. No adverse reprod/develop effects on reported	Oral gavage study (rat) NOAEL 95 mg/kg/day. No adverse reprod/develop effects on reported	1.2 mg/L	45 mg/L	6.2 mg/L	Readily Biodeg.
16	284	105-52-2	Maleic acid, bis(1,3-dimethylbutyl)ester	7.46 g/kg									
20	341	142-16-5	Maleic acid, bis(2-ethylhexyl)ester	> 10 ml/kg									
12	230	6938-94-9	Adipic acid, diisopropyl ester	> 15 g/kg (b)									
14	258	105-99-7	Adipic Acid, dibutyl ester	12.9 g/kg									
21	356	68515-75-3	Adipic acid, di-C7-9 branched and linear alkyl esters	>15.8 g/kg	90-Day Oral Diet (rat) NOAEL 1300 mg/kg Male NOAEL 1800 mg/kg Female	Negative (Ames)			Oral Gavage (rat) NOAEL 4000 mg/kg/day (Maternal and developmental)	> 1000 mg/L	1.9 mg/L	1.8-2.5 mg/L	
22	370	1330-86-5	Adipic acid, diisooctyl ester	45.0 g/kg (c)									Readily Biodeg. 86.7% in 28 days OECD 301B
22	370	108-63-4	Adipic acid, bis(1-methylheptyl)ester	> 64 g/kg									
22	370	103-23-1	Adipic acid, bis(2-ethylhexyl)ester	>7380 mg/kg	90-Day Oral (diet) LOAEL (rat) ~600 mg/kg/day; (mouse) ~460 mg/kg/day NOAEL (rat) ~300 mg/kg/day; (mouse) ~230 mg/kg/day	Negative (Ames, mouse lymphoma)	Negative (CHO in vitro; micronucleus, in vivo)	Oral Diet (rat) LOAEL = 1080 mg/kg/day NOAEL = 170 mg/kg/day	Oral Diet (rat) LOAEL = 1080 mg/kg/day NOAEL = 170 mg/kg/day	> 0.1 mg/L (d)	> 500 mg/L (d)	>100 mg/L (d)	Readily Biodeg
22	435	141-17-3	Adipic acid, bis[2-(2-butoxyethoxy)ethyl]ester										
24	399	33703-08-1	Adipic acid, diisononyl ester	>10 g/kg	90-Day Oral Diet NOAEL 500 mg/kg/day (rat) NOAEL 274 mg/kg/day (dog)	Negative (Ames, mouse lymphoma)				> 2.6 mg/L			Readily Biodeg. 73% in 28 days OECD 301F
26	427	27178-16-1	Adipic acid, diisodecyl ester	20.5 g/kg									Readily Biodeg. 68% in 28 days OECD 301F
32	511	16958-92-2	Adipic acid, ditridecyl ester	16 g/kg	90-Day Dermal (rat) Doses of 800 and 2000 mg/kg/d were well tolerated.	Negative (Ames)	Negative (micronucleus)	Dermal (rat) NOAEL = 800 mg/kg Sperm morphology, uterus+ epididymides weight-no effect		>5000 mg/L	4800 mg/L		Not Readily Biodeg 57% in 28 days OECD 301B
25	412	103-24-2	Azelaic acid, bis(2-ethylhexyl)ester	8.72 ml/kg						>1000 mg/L			Readily Biodeg. 81% in 28 days OECD 301B
29	469	28472-97-1	Azelaic acid, diisodecyl ester	>2 g/kg						>10,000 mg/L			Primary Biodeg
12	230	106-79-6	Sebacic acid, dimethyl ester										
26	469	122-62-3	Sebacic acid, bis(2-ethylhexyl) ester (c, e)	9.5 g/kg (mice) >12.8 g/kg (rat)	3-Week Oral Diet (rat) LOAEL 2% Diet (~1000 mg/kg/day) Liver weight increase and peroxisome proliferation reported 19-Week Orat diet (rat) NOAEL 200 ppm diet	Negative (Ames)		19-Week Oral Diet (Rat) NOAEL 200 ppm diet (~10 mg/kg/day) No adverse reprod effects		>1000 mg/L	>1000 mg/L	>1000 mg/L	Not Readily Biodeg. 65% in 28 days OECD 301B

Highlighted rows are not on the HPV list but included to facilitate category evaluation

(a) Toxicology data for dibuty maleate were reported in OECD SIDS dossier for Maleic acid, dibutyl ester (CAS 105-76-0). Also see IUCLID 1996 hedset

(b) LD50 value reported in Elder (1984). Final safety assessment of dioctyl adipate and diisopropyl adipate. Robust summary not prepared due to limited or insufficient information.

(c) LD50 value or toxicity findings reported in secondary reference (Patty's Toxicology, Chapter 79: David et al. 2001). Robust summaries were not prepared due to limited or insufficient information.

(d) No mortality in these aquatic species was observed at water saturation levels of test material.

(e) Toxicology data for di(2-ethylhexyl) sebacate have been reported in BIBRA Toxicology Profile (1996).

Table 3C. Group C - Aliphatic Esters, comprised of Monoacids and Dihydroxy Alcohols - "Glycol Esters"
Summary Table of Toxicology and Biodegradation Data

Total Carbon Number in Ester	MW	CAS Number	Chemical Name	Acute Oral LD50	Repeated Dose Toxicity	Genetic Tox (Point/Gene Mutation)	Genetic Tox (Chrom. Aber.)	Toxicity to Reproduction	Developmental Toxicity/ Teratogenicity	Acute Fish LC50 or LL50	Daphnia LC50 or LL50	Algal LC50 or LL50	Biodegradation %
15	258	71839-38-8	Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol	>2 g/kg	28-Day Oral Gavage (rat) Doses up to 1000 mg/kg were well-tolerated.	Negative (Ames)	Negative (human peripheral lymphocytes) No chrom aber.						Readily Biodeg. 87.3% in 28 days OECD 301B
20	329	111-60-4	Stearic acid, 2-hydroxyethyl ester	> 5 g/kg									
20	375	7434-40-4	Triethylene glycol, diheptanoate (a)			Negative (Ames)				>30 mg/L (>1000 mg/L with emulsifier)	9.1 mg/L	559-712 mg/L	65% in 28 days OECD 301B
21	343	1323-39-3	Propylene glycol, monostearate (b)	25.8 g/kg	6-Month Oral Study at 10% in diet No signs of toxicity in rats, dogs	Negative (Ames)							
22	419	70729-68-9	Heptanoic acid, oxybis(2,1-ethanediyloxy-2,1-ethanediyl) ester	25 g/kg	28-Day Oral NOAEL 1000 mg/kg	Negative (Ames)	Negative (CHO)			720 mg/L	3800 mg/L	16 mg/L	Readily Biodeg. 98% in 28 days OECD 301E
23	368	67989-24-6	9-Octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol (Monoester)	> 10 ml/kg							~ 2000 mg/L		Readily Biodeg. 73% in 28 days OECD 301B
24	431	68583-52-8	Decanoic acid, mixed diesters with octanoic acid and triethylene glycol										
24	447	18268-70-7	Hexanoic acid, 2-ethyl-, diester with tetraethylene glycol										
27	441	22788-19-8	Propylene glycol dilaurate (b)	> 34.6 g/kg (c)									
38	595	627-83-8	Stearic acid, ethylene ester (Diester)	> 16 g/kg									
39	605	105-62-4	Oleic acid, propylene ester (Diester)										
39	609	68958-54-3	Propylene glycol diisostearate (b)	> 25.8 g/kg (c)									
41	633	42222-50-4	9-Octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediyl ester (Diester)										

Highlighted rows are not on the HPV list but included to facilitate category evaluation

Footnotes:

a) Data for triethylene glycol diheptanoate based on IUCLID toxicology database for CAS 734-40-4.

b) Data for various ethylene or propylene glycol esters and their diesters were obtained from several references including: W Johnson, Internat. J Toxicol. 18 (Suppl. 2): 35-52 (1999) RL Elder, J. Amer. Coll. Toxicol. 1(2): 1-12 (1982); RL Elder, J. Amer. Coll. Toxicol. 2(5): 101-124 (1983).

c) Read across for the oral LD50 for the propylene glycol dilaurate was based on the LD50 for propylene glycol monolaurate; the diester was considered to be similar or less toxic than the corresponding monoester. similarly, the oral LD50 for propylene glycol distearate was based on its monostearate.

Table 3D. Group D - Aliphatic Esters, comprised of Monocids and Sorbitan - "Sorbitan Esters" Summary Table of Toxicology and Biodegradation Data

Total Carbon Number in Ester	MW	CAS Number	Chemical Name	Acute Oral LD50	Repeated Dose Toxicity	Genetic Tox (Point/Gene Mutation)	Genetic Tox (Chrom. Abs.)	Toxicity to Reproduction	Developmental Toxicity/ Teratogenicity	Acute Fish LC50 or LL50	Daphnia LC50 or LL50	Algal LC50 or LL50	Biodegradation %
18	346	1338-39-2	Sorbitan, monolaurate	36 g/kg	13-wk Feeding Study (Rat) LOAEL ~2200 mg/kg (2.5% diet)					75 mg/L			Not Readily Biodeg. 60% in 28 days OECD 301D (BOD)
18-20	346-374	68154-36-9	Fatty acids, coco, monoesters with sorbitan (main fatty acids are lauric and myristic acids)										
24	431	1338-41-6	Sorbitan, monostearate	> 15.9 g/kg	6-wk Feeding Study (Rat) NOAEL 2500 mg/kg/d (5% diet) 80-wk Feeding Study (Mice) NOAEL 2600 mg/kg/day (2% diet) 2-Yr Feeding Study (Rat) NOAEL 5000 mg/kg/d (10% diet)	Negative (Ames)	Negative (Hamster embryo cells in vitro)	In 2-yr feeding study in rats, no effect seen on gestation and fertility at 5, 10 and 20% in the diet. Survival of newborn and maternal lactation diminished at 20% in diet.					
24	430	1338-43-8	Sorbitan, monooleate	> 39.8 g/kg	16-wk Feeding Study (Rat) LOAEL ~1800 mg/kg/d (2.5% diet) 2-year Feeding Study (Rat) NOAEL (5%diet)					> 1000 mg/L			Not Readily Biodeg. 62% in 28 days OECD 301D (BOD)
33	569	8007-43-0	Sorbitan, sesquioleate	> 39.8 g/kg									
38	668	228573-47-5	Sorbitan, fatty acids C6-10, tetraester	>2.0 g kg	28-Day Oral NOAEL 1000 mg/kg (rat)	Negative (Ames)				>1000 mg/L	>1000 mg/L	>1000 mg/L	Not Readily Biodeg. 70% in 28 days OECD 301D (BOD)
60	958	26266-58-0	Sorbitan, trioleate	> 39.8 g/kg									

Highlighted rows are not on the HPV list but included to facilitate category evaluation

Table 3E. Group E - Aliphatic Esters, comprised of Monoacids amd Trihydroxy or Polyhydroxy Alcohols - "Polyol Esters"
Summary Table of Toxicology and Biodegradation Data

Total Carbon Number in Ester	MW	CAS Number	Chemical Name (Type Ester; Acid)	Acute Oral LD50	Repeated Dose Toxicity	Genetic Tox (Point/Gene Mutation)	Genetic Tox (Chrom. Aber.)	Toxicity to Reproduction	Developmental Toxicity/ Teratogenicity	Acute Fish LC50 or LL50	Daphnia LC50 or LL50	Algal LC50 or LL50	Biodegradation %
31	513	68130-53-0	Decanoic acid, mixed esters with heptanoic acid, octanoic acid and trimethylolpropane (TMP Ester; C7, 8, 10 Acid)										
			Trimethylolpropane esters of heptanoic and octanoic acid (TMP Esters; C7,8 acids)	Oral LD50 > 2000 mg/kg (rat)	28-Day oral toxicity (rat) NOAEL 100 mg/kg/day	Negative (Ames)	Negative Chrom. Aber.			>1000 mg/L	>1000 ppm	>1000 ppm	Not Readily Biodeg.
		71839-38-8	Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (TMP Esters; C7 acids)	Oral LD50 > 2000 mg/kg (rat)	28-Day oral toxicity (rat) well tolerated 1000 mg/kg/day	Negative (Ames)	Negative Chrom. Aber.			>1020 mg/L			Not Readily Biodeg.
		180788-27-6	Hexanedioic acid, mixed esters with C10-rich, C9-11 isoalcohols and TMP (TMP+other alcohols Mixed Esters; C6 dioic acids)	Oral LD50 > 2000 mg/kg (rat)	28-Day oral toxicity (rat) well tolerated 1000 mg/kg/day	Negative (Ames)	Negative Chrom. Aber.			>1000 mg/L	>1000 mg/L	>1000 mg/L	Not Readily Biodeg.
24	415	11138-60-6	Decanoic acid, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol octanoate (TMP Ester; C8, C10 Acid)	Oral LD50 > 5000 mg/kg (rat)	28-day Dermal (rat) NOAEL 2000 mg/kg/day	Negative (Ames)	Negative Chrom. Aber.	unpublished data will obtain copy of final report	unpublished data will obtain copy of final report	>1035 mg/L	>2570 ppm	>1018 ppm	Not Readily Biodeg.
33	555	126-57-8	Nonanoic acid, triester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (TMP Triester; C9 Acid)	Dermal LD50 2000 mg/kg			Negative Cytogenetic			>1000 mg/L	>9.3 mg/L	>4.4 mg/L	Not Readily Biodeg.
56	875	68002-79-9	Fatty acids, C14-18 and C16-18 unsatd, triesters with trimethylolpropane (TMP Triester; C14-18 satd, C16-18 unsatd Acid)										
24	417	70024-57-6	9-Octadecenoic acid (Z)-, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (TMP Monoester, Oleic C18 Acid)	Dermal LD50 > 10 ml/kg						2,027 mg/L			Readily Biodeg.
60	928	57675-44-2	9-Octadecenoic acid (Z)-, 2-ethyl-2-[(1-oxo-9-octadecenyl)oxy]methyl]-1,3-propanediyl ester, (Z)- (TMP Diester; Oleic C18 Acid)										Not Readily Biodeg.
33	529	67762-53-2	Carboxylic acids, C5-9, tetraesters with pentaerythritol (PE Tetraester; C5-9 Acids)	Oral LD50 > 1940 mg/kg (rat)		Negative (Ames)				>5012 mg/L			Not Readily Biodeg.
37	641	68130-51-8	Decanoic acid, mixed esters with heptanoic acid, isovaleric acid, octanoic acid and pentaerythritol (PE Mixed Ester; C7, 8 Acids)										
	613	68424-31-7	Fatty acids, C5-10, esters with pentaerythritol (PE Ester; C5-10 Acids)									>4.4 mg/L	
		68130-55-2	Hexanedioic acid mixed esters with decanoic acid, heptanoic acid, octanoic acid and PE (PE Mixed Esters; C6,7,8,10 acids)	Oral LD50 > 2000 mg/kg (rat)	28-Day dermal toxicity (rat) NOAEL 500 mg/kg/day	Negative (Ames)	Negative Chrom. Aber.			>5076 ppm	>5076 ppm	<324 ppm	Not Readily Biodeg.
41	697	14450-05-6	Nonanoic acid, neopentanetetrayl ester (PE Tetraester; C9 Acid)										
77	1202	115-83-3	Pentaerythritol, tetrastearate (PE Tetraester; C18 Acid)										

Total Carbon Number in Ester	MW	CAS Number	Chemical Name (Type Ester; Acid)	Acute Oral LD50	Repeated Dose Toxicity	Genetic Tox (Point/Gene Mutation)	Genetic Tox (Chrom. Aber.)	Toxicity to Reproduction	Developmental Toxicity/ Teratogenicity	Acute Fish LC50 or LL50	Daphnia LC50 or LL50	Algal LC50 or LL50	Biodegradation %
			Fatty acids, C5-9, esters with pentaerythritol (PE Esters; C5-9 acids)	Oral LD50 > 2000 mg/kg (rat)		Negative (Ames)							
	1100		Fatty acid, C6-10, tetraesters with PE (PE Tetraesters; C6-10 Acids)	Oral LD50 > 2000 mg/kg (rat)	28-Day oral toxicity (rat) NOAEL 1000 mg/kg/day	Negative (Ames)	Negative Chrom. Aber.			>5000 mg/L	>5000 mg/L	>5000 ppm	Not Readily Biodeg.
77	1188	68648-28-2	Linseed oil, ester with pentaerythritol (PE Ester: oleic, linoleic, linolenic C18 acids)	Oral LD50 > 5000 mg/kg (rat)									
77	1190	68334-18-9	Fatty acids, tall oil, tetra esters with pentaerythritol (PE Tetraester; oleic and linoleic C18 acids)										
60	927	70983-72-1	Fatty acids, C5-10, esters with dipentaerythritol (DiPE hexaester; C5-10 Acids)	Oral LD50 > 5000 mg/kg (rat)								>4.4 mg/L	
60	955	67762-52-1	Carboxylic acids, C5-9, hexaesters with dipentaerythritol (DiPE hexaesters; C5-C9 Acids)	Oral LD50 > 1940 mg/kg (rat)		Negative (Ames)				>5012 mg/L			Not Readily Biodeg.
			Fatty acids, C5-9, esters with dipentaerythritol (DiPE Ester; C5-9 acids)	Oral LD50 > 2000 mg/kg (rat)		Negative (Ames)							

Highlighted rows are not on the HPV list but included to facilitate category evaluation